THIOPENTONE

AND OTHER THIOBARBITURATES

BY

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TO MY WIFE

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PREFACE

Since the close of World War II intravenous anaesthesia has increased greatly in popularity and the majority of patients now expect to be given thiopentone or a similar drug Progress has not been limited to the clinical field and research workers have studied the action of the thiobarbiturates in detail In addition, new rapidly acting narcotics have been synthesised with the hope of overcoming some of the disadvantages of the earlier drugs Despite such advances, for more than a decade there has been no publication devoted solely to these agents, although it is in this period that most progress has been made

This book is intended for all physicians who are interested in intravenous anaesthesia. For the examination candidate and research worker the chemistry and pharmacology of the drugs is discussed in detail It is hoped that an unbiased view is presented of their various actions on which there is not, as yet, universal agreement.

The clinical use of intravenous anaesthesia cannot be discussed without reference to the recognised principles of general anaesthesia which apply to any agent. A detailed description of the latter subject is outside the scope of this work, but reference is made to the salient points which apply to the thiobarbiturates The essential facts attendant on a safe administration of thiopentone are summarised in a chapter which should prove invaluable to the beginner and the occasional anaesthetist. So that this section will be self-contained much repetition from other parts of the work is inevitable.

Judging by the number of new drugs which have been introduced in recent years, many advances in the field of intravenous anaesthesia are to be expected in the near future. It is even possible that the thiobarbiturates will lose their present day monopoly in this field and it is hoped that the information presented herein will help in the comparative evaluation of new compounds.

JOHN W DUNDEE.

Philadelphia 20,
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CHAPTER I

HISTORY

INTRAVENOUS INJECTION

THE distinction of being the first person to attempt an intravenous injection in man is usually ascribed to Christopher Wren Savillian Professor of Astronomy at Oxford University and architect of St. Paul's Cathedral London. His first attempts were with animals, and it is interesting to note that the first injection in man, about 1657 resulted in the unintentional production of unconsciousness. The apparatus consisted of a quill which was inserted into a vein, the injection being made through it either by using a small bladder as a pump or by means of a gravity feed.

The first resemblance to the modern syringe was the apparatus produced by Charles Gabriel Pravaz of Lyons about 1853 This was used for the injection of perchloride of iron into arteries for the cure of aneurysms. A fine gold or platinum trochar was introduced into the vessel and then attached to a syringe, the piston of which turned on a spiral thread. In 1861 Francis Rynd, a Dublin surgeon, described a method of introducing fluids to nerves for the cure of neuralgia and claimed to have used it since 1845 Macht (1916) considered Rynd's method to be the beginning of the modern hypodermic injection but according to Mogey (1953) it seems essentially to have been a trochar and cannula. However Rynd was probably the first to use a hollow hypodermic needle.

The piston of Pravaz and the needle of Rynd were first combined by Alexander Wood from Edinburgh in 1853 His object was similar to Rynd's, the results being published in 1855 under the title, New Method of Treating Neuralgia by the Direct Application of Opiates to the Painful Points The first injection consisted of the equivalent of about ⅖ gr (26 mg) of morphine hydrochloride and produced sleep for about 12 hours. Wood noted that the effects of narcotics thus applied were not confined to their local action, and commented that they reached the brain

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through the venous circulation and thereby produced remote effects.

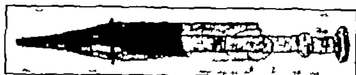


FIG 1 Alexander Wood's Syringe.
(Reproduced by permission of the Royal College of Physicians, Edinburgh.)
(Mogey 1953)

Wood's syringe consisted of a glass barrel, tapered to a point, with a metal nose-cap which was threaded externally to allow a hypodermic needle to be screwed on (Fig 1). The piston was wrapped round its extremity with cotton wick to make a tight fit for the barrel (Comrie, 1927) There are no accurate descriptions of the needle save that it had an aperture near the point which was likened to the sting of a wasp (Mogey has more correctly compared it to the sting of a bee, because of the barbs on the wasp's sting) The syringe was later improved by the addition of graduations to the barrel.

The screw piston, as devised by Pravaz, remained popular on the Continent until H W Luer introduced a metal and-glass instrument working on the push-pull mechanism of Wood's apparatus. He also abolished the screw mount for the needle and set the fashion for the hypodermic syringe as it is known today In 1896 Luer produced an all-glass model and ten years later the familiar Record syringe was made by a German firm (Mogey 1953)

Hypodermic injection of opiates as adjuvants to chloroform anaesthesia was introduced independently by Nussbaum of Munich and Claude Bernard in 1864 (Duncum, 1947) (However it was the work of Ehrlich with arsenicals in 1870 which showed the intravenous administration of drugs to be practicable, after which it became a common procedure in therapeutics)

EARLY INTRAVENOUS ANAESTHESIA

In his early experiments with intravenous injection Christopher Wren observed that a solution of opium when administered

intravenously to a dog stupefied but did not kill the animal. According to Keys (1941,42) Wren was probably unaware of the anaesthetic possibilities of the intravenous administration of opium. It would seem that the first deliberate attempt to produce intravenous anaesthesia was by Sigismund Elsholtz in 1665, an opiate being the solution used (Jarman 1946). The first transfusion of blood to animals is thought to have taken place in the same year, the credit usually being given to Richard Lower. Two years later Jean Baptiste Denys of France transfused lamb's blood to a man. As the result of fatalities from this procedure transfusion was prohibited by statute in France and Britain in 1670.

It was not until a quarter of a century after the discovery of the anaesthetic properties of ether and chloroform that any further interest was shown in intravenous anaesthesia. In 1872 Oré of Lyons produced anaesthesia in animals and man by the intravenous injection of chloral hydrate. His methods were not widely applied, and there were several unfortunate post-operative deaths. (Adams, 1944.)

The real beginning of practical intravenous anaesthesia was in 1905 when Krawkow and his co-workers in Russia, at what was then known as St. Petersburg, demonstrated the value of Hedonal. This drug (methyl propyl-carbinol urethane) had been introduced by Dreser of Munich in 1899. Hedonal proved to be moderately successful and for the next few years its use was reported sporadically in Europe. Its greatest popularity was in Russia, where in 1912 Federoff reported the use of the agent in 580 cases. The use of Hedonal spread to Germany and Britain where it was favourably received by Page and others (1912), but it was very little used in America.

The intravenous use of the volatile narcotics ether and chloroform, was first described by Burkhardt of Germany in 1909. Ether proved the more satisfactory agent, being used in a 5 per cent. solution in normal saline. Honan and Hassler (1924) reported 350 cases in which there were no deaths attributable to the method. Despite the satisfactory reports from workers in nearly every country the intravenous use of ether never became widespread. Burkhardt has also suggested the use of intravenous ether for maintenance of anaesthesia after induction with Isopral (trichlorisopropyl alcohol).

The use of intravenous paraldehyde was reported by Noel and

Souttar in 1913 It did not prove a great success, and repor its use in anaesthesia are few Peck and Meltzer reporte the production of anaesthesia by intravenous magnesium sulp in three cases in 1916, but this drug likewise did not a popularity Better results were obtained from ethyl alcohol w was used intravenously by Nakagawa in 1921 and Cardot Laugier in 1922 It enjoyed some popularity for a time in Me and in England its use in the latter country being reporte Constantin in 1929 and 1930. Apart from bromethol (Aver the intravenous use of which was described by Kirschner in 1 all further developments of intravenous anaesthesia concer the barbiturates.

For the sake of completeness reference must be made to production of local analgesia by the intravenous use of proca This was reported by August Bier in 1909 the solution being jected into a vein that had previously been rendered as bloodle possible and maintained so by the application of a tourniq A similar principle underlay the work of Goyanes of Madrid, in 1912 reported the use of intra-arterial procaine to ob analgesia of limbs.

BARBITURATES

The development of the barbiturates started with the s thesis of barbitone (di-ethyl barbituric acid) by Fischer and Mering in 1903 This was followed by phenobarbitone in 19 the intravenous use of which, as reported by Weiss in 19 was unsatisfactory The first barbiturate to receive any att tion as an intravenous anaesthetic was a combination of di-ethyl-amines of di-ethyl barbituric acid and di allyl barbit acid commonly known as Somnifen. It was first used ab 1920 and although moderately popular in France and Germ between 1924 and 1928 it was never much used in Britain America. Allyl isopropyl barbituric acid was introduced in 19 in an attempt to produce a drug of shorter action than Somnif and the intravenous use of a soluble preparation known as Nur or Alurate was described in 1927

Pernocton (sodium secondary butyl-β-bromallyl barbitura was the first barbiturate to be widely accepted as an intraven anaesthetic. Introduced by Bumm of Germany in 1927 it prov

to be shorter acting than Somnifen and for a time was popular as a basal narcotic in America. Although amylobarbitone (Amytal) had been synthesised by Shonle and Moment in 1921, its clinical use as a hypnotic was not reported until 1929 in which year Zefras and McCallum described the intravenous administration of its sodium salt. Lundy, of the Mayo Clinic, was largely responsible for popularising what proved to be the most satisfactory intravenous anaesthetic at that time, and amylobarbitone was extensively used in America and Britain between 1929 and 1933 Pentobarbitone, prepared independently by Volwiler and Tabern and by Sholne and his colleagues in 1930, proved to be equally satisfactory as a narcotic, and Fitch, Waters and Tatum described its intravenous use in that year It was first known as Embutal from the initial letters of its chemical name [1] the soluble sodium salt being called Nembutal. Amylobarbitone and pentobarbitone still enjoy a limited popularity as intravenous anaesthetics, but their use is now mainly limited to psychiatry, basal narcosis and in combination with spinal or local analgesia

After a brief visit to America the progress of intravenous anaesthesia again reverted to Germany, where Kropp and Taub working under the direction of Weese, produced hexobarbitone. Weese and Scharpff published the first report on this drug in 1932. The use of Evipan as it was then called rapidly spread to the rest of Europe, Jarman and Abel reporting its use in Britain in 1934. Its success as an anaesthetic can be judged from the fact that in 1944 Adams estimated that the number of administrations up to that time was well over 10 000,000 Until the introduction of thiopentone, hexobarbitone was by far the most satisfactory available intravenous anaesthetic agent.

A few other barbiturates have been tried as intravenous anaesthetics but without much success The use of butobarbitone (Neonal Soneryl) was described in 1934 and ethyl Soneryl in the following year Eunarcon (sodium isopropyl β-bromallyl N methyl barbiturate) was introduced in Germany two years after hexobarbitone, and, apart from being available in an aqueous solution had no advantage over the latter drug In 1936 Thalheimer described the clinical use of Narconumal or Methyl Numal (sodium methyl allyl isopropyl barbiturate). This pre-

[1] *-al* is the American ending for barbiturates in place of the British *-one* e.g barbital barbitone

paration, which bears some similarity to hexobarbitone, has been fairly widely used in Europe, but could not compete with the growing popularity of thiopentone.

THIOBARBITURATES

Early in the history of barbituric acid synthesis two or three simple 5 5 di-substituted 2 thio derivatives were made, with the aim of preparing from them, by removal of the sulphur atom, the therapeutically active oxygen analogues. In 1911 Johnson and Hill reported the synthesis of sulphur-containing barbiturates, but little attention was paid to this work. Tabern and Volwiler (1935) prepared a large number of these compounds about 1934. They found that the thio-analogues of those di-substituted barbiturates previously found most valuable as hypnotics ranked highest in efficiency and concluded that the sulphur atom seemed to shorten the period of destruction within the body and hence led to a briefer duration of hypnosis.

THIOPENTONE

Many of the thiobarbiturates described by Tabern and Volwiler have since proved to be of great clinical interest, although the drug which was most satisfactory in the early trials and which has since attained the greatest popularity is thiopentone.

Clinical trials of thiopentone as an intravenous anaesthetic were started in 1934 by J S Lundy of the Mayo Clinic and by R. M Waters at Wisconsin General Hospital. Lundy and Tovell (1934) referred to the drug as Thionembutal and in the first detailed report on its use by these workers it was called Barbiturate A Pratt, Tatum, Hathaway and Waters described their experimental and clinical findings in 1936 referring to thiopentone as # 8064

The drug was marketed in the United States as Pentothal in 1936 and received the generic term thiopental. It was accepted by the American Medical Association Council on Pharmacy and Chemistry in 1939 and was included in the 13th edition of the United States Pharmacopoeia.

Thiopentone was introduced in Britain by Jarman in 1935 and two communications on its use were published by Jarman and

Abel in 1936 the drug then being called 'Pentothal' It has been manufactured in this country since 1937 A monograph first appeared under the Latin title "Thiopentonium Solubile" in the seventh addendum to the 1932 issue of the British Pharmacopoeia and thiopentone became an official B P preparation in 1945 In 1936 van der Post introduced thiopentone into South Africa, while early reports on its use in Canada came from Heard (1936), and in Australia it was popularised by Brown and Troup (1938).

The popularity which thiopentone gained as an intravenous anaesthetic is shown by the first detailed reports of its use by Lundy (1935) which dealt with 700 administrations of the drug while Jarman and Abel (1936) reported over 1000 administrations. By the end of 1935 the number of patients anaesthetised with thiopentone at the Mayo Clinic totalled 1333 the figure by the end of 1936 being 2745 However the studies of its pharmacological action did not keep pace with the clinical work and the only notable contributions during the first two years after the introduction of thiopentone were those of Werner and Pratt (1936) and Pratt, Tatum, Hathaway and Waters (1936)

DEVELOPMENT OF THE USE OF THIOPENTONE

An analysis of the anaesthetics administered to over three million patients during the years 1934 55, reveals that over one-third of all cases received thiopentone (Table I), and that almost half of the patients had some form of intravenous anaesthesia.

TABLE I

The incidence of the use of thiopentone and other intravenous anaesthetics during the years 1934 55 collected from sources all over the world

		Percentage Total Cases	*Percentage General Anaesthetics*
Total anaesthetics	3,415,408	—	—
General anaesthetics	2,748,820	80·47	—
Intravenous anaesthetics	1,256 759	36·80	45·73
Thiopentone	1 179,934	34 55	42·93
Other intravenous	76,825	2·25	2·80

These figures were obtained from hospital records, publis papers and personal records of various anaesthetists. They be further analysed to show the development of the use of th pentone in different countries during the years under study

Great Britain. Records of in-patient anaesthetics from hospitals, which it is hoped will be representative of the coun as a whole (Table II), were studied in detail. In each hosp

TABLE II

Details of hospitals from which the anaesthetic records were analysed in detail

District	*Teaching*	*No of Hospitals*	*Total No. of Beds*	*Average Numb of Anaesthetic per Year*
London	Yes	3	1 703	14,853
London	No	3	1 909	12,186
Provinces	Yes	4	1 704	8 742
Provinces	No	4	2,453	10 173
Scotland, Wales, Northern Ireland and Isle of Man	Yes	3	1,942	7 190
Scotland, Wales, Northern Ireland and Isle of Man	No	5	1,880	7,009
Total	—	22	11,591	60,153

the percentage of patients receiving thiopentone, other intraveno barbiturates and unsupplemented local or spinal analgesia w calculated for each year between 1934 and 1954. In 18 of the hospitals the incidence of the use of muscle relaxants was al analysed for each year up to and including 1951 The ear records were incomplete in a few hospitals, and in two instanc the figures for 1940 to 1944 had been destroyed during air raid In order to compensate for the different total number of anae thetics administered in different hospitals, the average w calculated from the percentage of the administrations of eac agent in each hospital per year rather than from the total figure from all hospitals for each year

In another series, which includes the above, data were obtaine from various sources. This is not as representative as the figure from the selected hospitals since records from some of the sources

TABLE III

Incidence of administration of thiopentone in Great Britain during 1934 55 Figures for the latter year only include administrations up to the end of March

Year	Selected Hospitals					All Sources		
	Total Cases	Percentage of Total				Total Cases	Percentage of Total	
		General Anaesthetics	Thiopentone	Other Intravenous	Relaxants		Thiopentone	Other Intravenous
1934	42,489	81 57	—	2·75	—	143,921	—	3·79
1935	39,612	87·29	—	3·46	—			
1936	44,312	85·79	0·37	4·77	—	140 193	0·79	5·06
1937	41 315	86·82	1 48	4·04	—			
1938	46,808	86·15	2·42	3·65	—	143,145	4 27	4 38
1939	45 592	84 21	4·34	3·09	—			
1940	38,300	82·89	5·43	1 86	—	135 372	5·41	2·72
1941	46,090	84 10	6·38	3·06	—			
1942	49,383	83·03	8·22	4·79	—	156,808	7·64	7·03
1943	47 547	85·30	9·54	6·71	—			
1944	42,160	84 10	11·69	5·74	—	138,509	18 19	4·01
1945	42,585	81 15	16·52	2 15	0·82			
1946	48,214	83·96	32·61	2·97	1 80	170,259	45·94	1·36
1947	56 969	84 48	48 28	1 35	7·40			
1948	64,909	86·76	53 10	2·08	9·79	217,245	57·24	1·67
1949	67 062	87·10	62·76	1·61	12·43			
1950	70,577	90·29	69·85	2·03	19·96	227,607	68 13	1·94
1951	61 805	91 10	73·79	2·25	27·28			
1952	72,708	89·56	77·69	1 83	—	254 350	74·94	1·66
1953	69,425	89·86	76·38	1·71	—			
1954	57,203	91·99	80·30	2·88	—	131,227	79·74	2·44
1955	—	—	—	—	—			
Total	1,095,065	—	—	—	—	1,858,636	—	—

including those from individual anaesthetists, deal only with a few of the years under study These figures were analysed in two-year periods, and the incidence of administration of the various agents was calculated from the total number of cases for each two-year period.

Table III shows the result of this study and Fig 2 illustrates the incidence of the use of thiopentone and other agents in both series. Although introduced as an intravenous anaesthetic in 1935 the use of thiopentone increased very slowly until 1946. Over the next five years it increased greatly in popularity and at present it is used in over 80 per cent. of all anaesthetics in Great

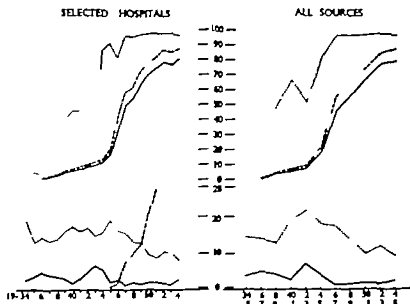


FIG. 2. The percentage use of thiopentone and other agents in Great Britain from 1934 1955.

Upper graph.
—— Thiopentone as percentage of total anaesthetics.
Thiopentone as percentage of total general anaesthetics.
Thiopentone as percentage of total intravenous anaesthetics.

Lower graph.
—— Percentage use of other intravenous agents.
Percentage use of unsupplemented local and spinal analgesia.
Percentage use of muscle relaxants.

Britain. The early slow development may have been partly due to shortage of supply of the drug during the war years. The return of large numbers of skilled and experienced anaesthetists to civilian practice was in part responsible for the post war popul

arity of thiopentone Another reason for this was the introduction of muscle relaxants which allow a light (and safe) plane of barbiturate narcosis to be maintained with adequate relaxation for major surgical operations

Although it is not shown in either Table III or Fig 2, thiopentone was first adopted for routine use in the London and English provincial teaching hospitals The non teaching hospitals in these centres began using the drug long before its introduction in Scotland or Northern Ireland In some of the smaller hospitals in the latter countries thiopentone was used for the first time about 1945 46

It can be seen that neither hexobarbitone nor thialbarbitone has attained any great popularity in this country Although the other intravenous agents used in the post war years consist almost entirely of thialbarbitone hexobarbitone has not been completely abandoned

America. Forrester (1950) has pointed out that the anaesthetic agents and techniques used in the United States vary greatly from place to place. In contrast with this country, there is no generally adopted technique, which varies only slightly with different administrators

In Fig 3 is shown the incidence of the administration of thiopentone and other agents at the Mayo Clinic (where thiopentone was first popularised) during the years 1934 53 (Mayo Clinic Reports, 1934 53) This shows two great differences from the British figures (Fig 2) in that the drug was more widely used in the pre-war period than in Britain [1] and that its present use at the Mayo Clinic is not as widespread as in this country This latter may be due to the fact that the total number of anaesthetics administered in this American hospital may include out patients, who are unlikely to receive thiopentone. Furthermore, Fig 3 shows a decline in the use of thiopentone after 1941, and it was not until 1947 that the percentage of patients receiving the drug exceeded the 1941 figure.

[1] That this rapid increase in the use of thiopentone was not limited to the Mayo Clinic is shown by reports from other centres. In 1939, Ruth, Tovell Milligan and Charleroy published a paper entitled "Pentothal Sodium, Is its Growing Popularity Justified?" They reviewed reports of 21,344 administrations and analysed 2980 in detail concluding "In view of its apparent effectiveness and safety its growing popularity is warranted and further exploration for possible application among the groups of patients now receiving inflammable anaesthetic agents by inhalation seems justified

being employed in 65 per cent. of cases, as compared with 9 per cent. for thiopentone. Data from the Middle East are also not available, but thiopentone is used for the induction of anaesthesia for thoracic surgery at the Farouk University Hospitals, Alexandria (Nassar 1952)

Personal observations have shown that thiobarbiturates are widely used in Argentine. Their incidence is probably not much less than the present day use in Britain. This also applies to Chile and surrounding countries in South America.

Military Surgery In Table IV is shown a representative selection of published figures illustrating the incidence of the use of thiopentone during the Second World War Most of these deal with the United States Armed Forces, by whom the drug was employed in between one-third and one-half of all cases. Its use by the Canadian Forces seems to have been slightly greater

The use of thiopentone by British Forces is illustrated by the following reports from the *History of the Second World War* United Kingdom Medical Series

Discussing the treatment of war wounds in general, Porritt (1953) remarks Undoubtedly the great stand by was intravenous pentothal. This proved the greatest boon to patients who were scheduled for a series of operations.

In the Army A survey of anaesthetics used in North Africa and Italy during the winter of 1943 44, showed that in both rear and forward areas, over 80 per cent. of operations were performed with pentothal, either as the sole agent or as a preliminary anaesthetic. This number increased to well over 90 per cent. towards the end of the war

The immeasurable value of intravenous anaesthesia—which in practice meant pentothal sodium—made the anaesthetist's work so much more expeditious that on all sides could be heard the question What would we do without pentothal? (Daly 1953).

Of anaesthesia in the Royal Navy Woolmer (1953) writes a combination of circumstances clearly points to regional or intravenous anaesthesia as the method of choice in most cases the development of the intravenous route represents, by far the greatest advance in war-time anaesthesia since 1914 18 and it has enabled medical officers to undertake tasks which would have been beyond their scope in the war of 1914 18. Even so, reports indicate that its use has not been so extensive as might have been expected.

In the Royal Air Force medical services "Pentothal was universally popular in the field, particularly for wounds of the limbs and for minor surgical procedures. In war its advantages certainly outweighed its main disadvantage" (Macintosh, 1953).

These quotations suggest that thiopentone was more widely

TABLE IV.—*Representative figures of the incidence of the use of thiopentone in military surgery*

Forces	*Place*	*Time*	*Incidence of use of Thiopentone* — *% of Cases* — *Used alone*	*In combination*	*Total*	*Ref*
A. COMBAT ZONE						
United States	European Theatre of Operations	January–June 1943	22·07	9·98	33·06	1
		June–October 1944	39·51	11·34	50·85	
		Nov. and Dec. 1944	37·82	14·59	52·41	
		January–June 1945	30·72	17·15	47·87	
United States	Unspecified	Unspecified	32·41% of all cases			2
United States	Forward Hospitals (Unspecified)	1943	53% of all cases			3
		1944	62% of all cases			
United States	New Guinea	1943–44	32·8% of all cases			4
			38·5% of general anaesthetics			
United States	Okinawa	—	29% of all cases			5
United States	Italy	—	5·9% of all cases			6
			6·2% of general anaesthetics			
Canadian	Normandy	First 100 days after invasion	87% of all cases			7
United States	South Pacific—on board ship	1942	5·8% of all cases			8
			62% of general anaesthetics			
B. EVACUATION AND BASE HOSPITALS						
United States	Pacific Coast and Atlantic Seaboard	1941–43	11·1% of all cases			9
			15·1% of general anaesthetics			
United States	Unspecified	1943	28% of all cases			3
		1944	48% of all cases			
United States	Unspecified	—	87% of all cases			10
Canadian	Borden Military Hospital	—	35% of all cases			11
Canadian	Base Naval Hospital	1943	33% of all cases			12
			59% of general anaesthetics			
British	Maxillo-facial Unit	—	99% of all cases			13
United States	Naval Airforce Hospital	1943–44	27% of all cases			14
			86% of general anaesthetics			

References.—1 Tovell (1947) 2. Shorts (1944) 3 Bull. U.S. Army Med. Dep. (1945); 4 Hampson and Hammet (1945); 5 Coakley (1946); 6 Bowers (1945); 7 Wainwright (1945); 8 Ferguson (1944) 9 Rose (1943) 10. Wangeman and Martin (1945) 11 Boddington (1944) 12 Stoddart (1944) 13 Roche (1946) 14 Ruzicka (1945).

used by the British than by the American Forces during the Second World War They also support the view that the great increase in popularity of thiopentone in the immediate post war period was due to the return to civilian life of anaesthetists who had gained considerable experience with the use of the drug in the Armed Forces.

Overall Use. Table V shows data of the incidence of the use of thiopentone collected from all available sources outside Britain

TABLE V

Incidence of the use of thiopentone in hospitals outside Britain from the beginning of 1934 to the end of March 1955

Years	*Sources outside Great Britain*			*All Sources*		
	Percentage of Total			*Percentage of Total*		
	Total	*Thio-pentone*	*Other Intravenous*	*Total*	*Thio-pentone*	*Other Intravenous*
1934 35	38 951	3·62	0·02	182,872	0·77	3·02
1936-37	42,762	16·30	0·01	182,955	4 19	3·90
1938-39	28,542	38·62	0·03	171 687	10·00	3·70
1940-41	52,464	28 44	1·00	187,846	11 84	2·24
1942-43	74,482	29·04	0·91	231,290	14 53	4 85
1944-45	99,313	34 83	0·01	237,822	25 14	2·34
1946-47	70 908	36·25	0·01	241 167	43·09	1·05
1948-49	316 712	25·27	0·03	535,957	39·26	1·61
1950-51	371,406	30·73	0·02	599,013	44·94	1 57
1952-53	237,278	39·58	2·01	491 628	57·87	1 83
1954 55	—	—	—	131,277	79·74	2·44
Total	1,332,818	—	—	3 193 514	—	—

and the incidence of its use all over the world from 1934 55 This latter is shown graphically in Fig 4. There are over 300 000 anaesthetics analysed in Table I which do not appear in Table V This is due to the fact that, although the incidence of the use of the various agents was known in these cases, the exact date of the administration was not available.

Publications. Fig 5 shows the number of publications concerning the use of thiopentone in the library of Abbott Laboratories, North Chicago There are two periods during which the literature on the drug increased rapidly the first (1944 45) was at the end of the last war and the second (1950-51) followed the general world wide acceptance of muscle relaxants in anaesthesia.

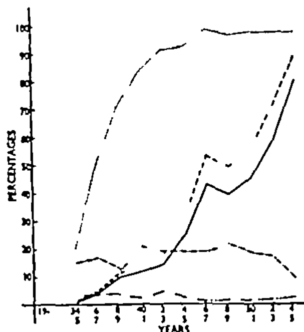


FIG. 4. Percentage use of thiopentone and other agents in hospitals all over the world (1934 1955)

—— Thiopentone as percentage of total anaesthetics.
Thiopentone as percentage of general anaesthetics.
Thiopentone as percentage of total intravenous anaesthetics.
- - Unsupplemented local and spinal analgesia.
Other intravenous agents.

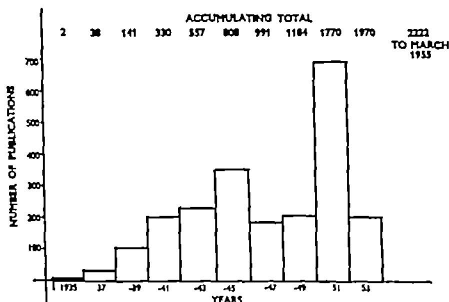


FIG. 5 —Number of publications on thiopentone at the library of Abbott Laboratories, Chicago.

THIAMYLAL

Thiamylal was first mentioned in 1935 in the studies of sulphur containing hypnotics by Tabern and Volwiler which preceded the introduction of thiopentone. A method of synthesis was perfected by Dox, and a United States patent was granted on 11th April 1939 (Dornette, 1954) Development of the drug was held up by the Second World War but interest was revived about 1944. Four years later Reutner and Gruhzit reported an extensive series of investigations in laboratory animals, and in 1949 Wyngaarden, Woods, Ridley and Seevers reported its anaesthetic properties in the dog

Following favourable clinical reports by Helrich, Papper and Rovenstine and others in 1950 the drug was released for clinical investigation under the name of Surital Sodium. It was accepted by the Council of Pharmacy and Chemistry (U S.A.) in 1951 and given the generic name of thiamylal sodium, under which name it was included in New and Non-official Remedies in 1952.

In June 1951 Lund reported on a series of 700 administrations of thiamylal, his series having increased to 4700 cases by the time the report was published. Many other extensive series of cases were reported in the United States about the same time. By October 1951 Lund had administered the drug to 6000 consecutive patients, and when details of these appeared in the literature early in 1954, the numbers exceeded 15 000 administrations.

The use of thiamylal as an intravenous anaesthetic has not progressed so quickly in Britain as in the United States. Barran and Wylie reported on its use in a small series of patients in 1951 In their report the drug was referred to as thioquinalbarbitone. No further mention of thiamylal appeared in Britain until 1955 when 400 administrations were recorded by Jolly and Lederer and Dundee and Riding reported on its use in over 1700 cases. At the time of writing thiamylal is not commercially available in Britain.

THIALBARBITONE

Thialbarbitone was synthesised by Carrington in 1938 during a search for a new intravenous anaesthetic similar to but having advantages over thiopentone. Its pharmacology was investigated

by Carrington and Raventós and reported in 1946. Results of clinical trials by Macintosh and Scott (400 cases), Gordon and Gibbons (372 cases) and Halton (1000 cases) appeared in the same year. Early reports were mostly limited to its use in Britain, the first French paper by Jacquot, Roux and Huguenard appearing in 1949. In 1949 its use was also described in South Africa by Widgerow. Although not having attained the popularity of thiopentone, thialbarbitone is available commercially in all countries except Russia and the United States.

In early papers the drug was known as Kemithal. The generic name 'thialbarbitone' was accepted by the British Pharmaceutical Commission in 1947, and appeared in the *British Pharmacopoeia Codex* in 1954. Its use in veterinary anaesthesia is shown by the fact that three monographs on this subject appeared in the *British Veterinary Codex* of 1953.

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CHAPTER II

PHYSICAL PROPERTIES AND CHEMISTRY

THE sodium salts of thiopentone, thiamylal and thialbarbitone are the thiobarbiturates in most common clinical use.* The various names by which these preparations are known and details of their oxygen analogues are shown in Table VI. Their chemical structures and the melting points of the free acids are given in Table VII.

TABLE VI

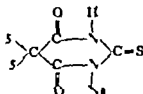
Synonyms of the three thiobarbiturates in common use

Official Names	*Proprietary Names*	*Oxygen Analogue*
Thiopentone Soluble (B.P.) Thiopental Soluble (U.S.P.) *Penthiobarbital* (France)	Pentothal Sodium (Abbott English-speaking countries) Intraval Sodium (May & Baker) *Nesdonal* (Specia) Penthiobarbital Sodique (Abbott France) Trapanal (Promonta Werk Hamburg) Farmotal (Farmitalia Milan) Thionembutal (Abbott Brazil) Pentothal Natricum) Abbott: *Norway)* Pentothal Sodico (Abbott Spanish-America)	Pentobarbitone (B.P.) Pentobarbital (U.S.P.) *Synonym* Nembutal
Thiamylal (U.S.P.)	Surital Sodium (Parke, Davis) Thio-Seconal (*Lilly*)	Quinalbarbitone (B.P.) Secobarbital (U.S.P.) *Synonym* Seconal
Thialbarbitone Sodium (B.P.C.)	Kemithal (I.C.(P.) Ltd.) *Kemithene (do. Chile)*	Not available commercially

* For the sake of simplicity the term *thiopentone* is used throughout the text to refer to the soluble sodium salt. This terminology is also used for the other barbiturates.

TABLE VII

Chemical structure of the thiobarbiturates in common use

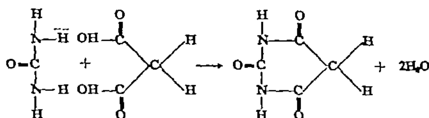


	5	5	Melting point Free Acid C
Thiopentone	$CH_3 CH_2$—	$CH_3 CH_2 CH_2$—CH—(CH_3)	158—159
Thiamylal	CH_2=CH CH_2—	$CH_3 CH_2 CH_2$—CH—(CH_3)	127—134
Thial barbitone	CH_2=CH CH_2—	CH_2<(CH_2—CH)(CH_2—CH_2)>C—	142

Thiopentone Sodium 5-ethyl 5 -(1-methylbutyl)-2 thiobarbiturate
Thiamylal Sodium 5-allyl-5 -(1-methylbutyl)-2 thiobarbiturate.
Thialbarbitone Sodium 5-allyl 5'-cyclohexenyl 2 thiobarbiturate

The sodium salts of the thiobarbiturates are pale yellow hygroscopic powders with a bitter taste, which are readily soluble in water partly soluble in 95 per cent. alcohol and insoluble in solvent ether and benzene. The oil/water partition coefficient of thiopentone is about 4·7 as compared with 2·9 for amylobarbitone and 0·214 for barbitone. Commercial preparations of thiopentone and thiamylal contain a mixture of 100 parts by weight of the sodium salt of the thiobarbiturate and six parts by weight of exsiccated sodium carbonate. This latter prevents precipitation of the insoluble free acid by atmospheric carbon dioxide. The British Pharmacopoeia (1953) standard for soluble thiopentone requires the preparation to contain 84 to 87 per cent. $C_{11}H_{18}O_2N_2S$ and 10 to 11 per cent. sodium, both calculated with reference to the substance dried to a constant weight at 70° C and at a pressure not exceeding 5 mm. Hg

Synthesis. The basic chemical reaction for the synthesis of all barbiturates is as follows



Urea and malonic acid→barbituric acid (or malonyl urea)+water

Barbituric acid is inert and has no hypnotic property, but substitution of the hydrogens by organic radicals (aliphatic, aromatic or heterocyclic) gives the resultant barbiturate a narcotic effect. Thiobarbiturates are prepared by using thiourea, rather than urea, in the above compounds.

There are two standard methods for making thiobarbiturates, such as thiopentone

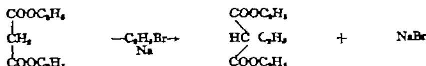
(1) by the *malonate route* and

(2) by the cyanacetate route.

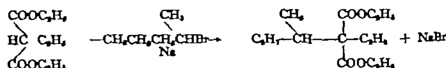
Both are used for commercial manufacture and have certain features in common.

1 The Malonate Route

(*a*) Diethyl malonate is mono-alkylated at the 2 position with ethyl bromide in the presence of sodium ethoxide

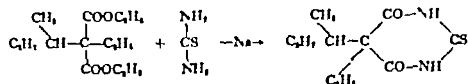


(*b*) The diethyl ethyl malonate is then alkylated with 2-bromopentane under conditions similar to those described under (*a*) above



(*c*) The purified 1 3 diethyl 2-(1-methylbutyl-ethyl) malo-

nate is condensed with thio urea in the presence of sodium ethoxide



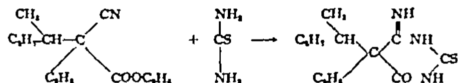
The pure acid is precipitated from an aqueous solution of the reaction mixture by the addition of mineral acid, filtered off and dried

(*d*) The dried acid is dissolved in alcohol containing the appropriate quantity of sodium to form a solution of the sodium salt. This is precipitated by the addition of a suitable solvent, filtered off, dried and mixed in the ratio of 100 6 with sodium carbonate.

2 THE CYANACETATE ROUTE

(*a*) and (*b*) The first two stages are analogous to the malonate route, leading to ethyl 1 methylbutyl ethylcyanacetate.

(*c*) Condensation with thio-urea in the presence of sodium ethoxide in this case gives an imide



(*d*) This imide is suspended in dilute mineral acid and heated, to give the same end product as in 1 (*c*)

(*e*) The preparation of the product for injection is exactly as described in 1 (*d*).

(**Solutions.** Aqueous solutions of thiobarbiturates for intravenous anaesthesia are strongly alkaline, the *p*H of 2 5 per cent. thiopentone being about 10·5) The strengths of solutions commonly used for intermittent injection vary between 2 and 5 per cent. with thiopentone and thiamylal and between 2 and 10 per cent. with thialbarbitone. For continuous infusion 0·2 to 1 per cent. solutions are generally used. The compatibility of a 2·5 per cent. solution of thiopentone with various drugs which are likely to be used in anaesthesia is discussed in Appendix 2. The average time taken by various commercial preparations for

complete solution to various strengths under standard conditions, similar to those used in clinical anaesthesia practice, are shown in Table VIII Thus thiamylal is slightly more soluble and thialbarbitone appreciably less soluble than thiopentone.

TABLE VIII

Comparison of the rates of solubility of various thiobarbiturates and barbiturates used in anaesthesia, and of different strengths of solution of the same barbiturate

(Dundee, 1954)

Drug	*Proprietary Name*	*Per centage Solution w/v*	*Solubility Time (mins.)*		*Relationship to average of Intraval and Pentothal*
			Average	*Range*	
Thiopentone	Intraval	5	9·40	7·75—12 50	—
	Pentothal	5	9·28	7·00—12·00	—
	—	5	12 51	9·00—15·00	1·34
Thialbarbitone	Kemithal	10	37·03	26·00—47·00	3·95
	Kemithal	5	11 43	8·75—14·00	1·22
Thiamylal	Surital				
	bottles	5	5·68	3·50— 7·50	0·61
	ampoules	5	6·60	5·00—12·00	0·70
Hexobarbitone	Evipan	10	18 87	10·50—33·75	2·00
	Evipan	5	10·64	6·25—14·25	1 14
	—	10	9·40	6·00—16·00	1·06
	Cyclonal	10	5·00	4·00— 6·00	0·53

(**Stability** Atmospheric carbon dioxide will readily precipitate the free acid from an aqueous solution of sodium thiopentone. For this reason the commercial product is packed in sealed ampoules in an atmosphere of nitrogen. Stored solutions must also be protected from the atmosphere.)

The 5 per cent. solution rapidly deteriorates at room temperature, but this can be reduced by storage in a refrigerator at 5° to 6 C. Robinson (1947) has examined the stability of the drug under the above conditions. At 18 to 22 C particles appear in the solution about the third day and this coincides with a fall of 1° in the melting-point of the extractable thiopentone acid. At 5 to 6 C the appearance of particles in the solution is delayed up to the eighth day and a fall in melting point does not appear until about the fifteenth day This work suggests that as long as

the solution is clear it is fit for clinical use. However, since turbidity may be difficult to detect in a poor light solutions should be discarded after three days if kept at room temperature or after seven days if stored in a refrigerator

Detection and Estimation. Thiopentone can be detected and estimated quantitatively by colorimetric methods, by ultra violet spectrophotometry or by physical methods Unfortunately some of the methods that have been described in the literature are not specific for thiopentone. Many give positive results with any barbiturate or even with their breakdown products This applies particularly to the colorimetric methods of analysis, which depend upon the interaction of barbiturates and thiobarbiturates with cobalt salts in an alkaline medium or of copper salts and thiobarbiturates. Raventós (1954) has pointed out that in addition the ether or chloroform extracts of tissues and urine may contain impurities which give a positive reaction with cobalt or copper

Modern methods of analysis depend on the fact that the ultra-violet spectrum of thiobarbituric acids has a maximum at about 290 mμ when examined in acid media and about 305 mμ in alkaline media. The intensity of absorption of ultra violet light by a tissue extract at those wavelengths may be used as a measure of the thiobarbiturate content of the sample. Hellman Shettles and Stan (1943) were the first to describe a spectrophotometric method for the estimation of thiopentone in blood They utilised a characteristic absorption band at 288 mμ in ether solution This was modified by Jailer and Goldbaum (1946) who employed chloroform for the extraction and read the results at 285 mμ. The sensitivity of their method was somewhat increased by extracting the chloroform layer again with sodium hydroxide, readings being made at 305 mμ. Using this technique with several barbiturates Goldbaum (1948) found that the lowest limit of detection was 0·4 mg per 100 ml of blood and 1 0 mg per 100 g of tissues, with an error of less than 10 per cent.

While the spectrophotometric methods of assay of thiopentone are more accurate than colorimetric methods, they are not completely specific. The ultra violet spectrum of all thiobarbiturates and some of their metabolites is identical as long as the ring structure remains intact (Raventós, 1954) To be absolutely specific, methods of extraction of biological material must be used which will remove only the thiopentone without extracting its metabolites

CHAPTER III

DISTRIBUTION AND FATE IN THE BODY

DISTRIBUTION IN THE BODY

Experimental Data. Early reports on the use of thiopentone suggested that the drug was rapidly broken down in the body, as expressed by the terms short acting and ultra-short acting by which the thiobarbiturates used in anaesthesia are commonly referred to in the literature. Despite this terminology isolated clinical reports of prolonged narcosis after thiopentone appeared from time to time In 1938 Veal and Reynolds pointed out that the repeated injections of small fractional doses of the drug were not comparable with the administration of ether by the open-drop method. Animal experiments showed that thiopentone had a marked cumulative action, the repeated administration of doses of the same amount resulting in a gradual prolongation of narcosis with each successive dose (Reynolds, 1939) More recently Wyngaarden *et al.* (1949) have confirmed these findings and also shown that they apply to thiamylal and thioethamyl.

To explain the cumulative action of thiopentone and the prolonged narcosis which follows large total doses, Reynolds (1939) postulated that normal organs are incapable of destroying more than a certain amount of the drug He also suggested that thiopentone caused liver dysfunction the initial dose thereby reduces the ability of this organ to deal with supplementary doses. Another explanation, mentioned by Maynert and Van Dyke (1949) was that the breakdown of thiopentone may involve the formation of a longer acting barbiturate such as pentobarbitone.

Until about 1948 it was believed that the duration of action of thiobarbiturates was determined by the rate of their metabolic transformation. A clearer understanding followed the perfection of techniques for the quantitative determination of these drugs in plasma and tissues. Brooks *et al.* (1948) were the first to show that rapid diffusion of thiopentone to non nervous tissues occurred and was responsible for the short action of small doses. Many other studies have followed and, due largely to the work of Brodie

and Shideman and their colleagues, new light has been thrown on this subject.

[After a single intravenous injection of thiopentone in man the plasma concentration falls rapidly for the first 15 to 30 minutes and thereafter the decline is more gradual (Fig 6) This early

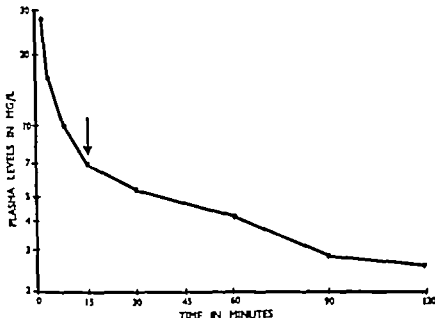


FIG. 6—Plasma levels of thiopentone in man after the intravenous administration of 400 mg in two minutes.
Arrow indicates point at which the subject wakened.
(Brodie, Mark, Papper Lief Bernstein and Rovenstine, 1950)

fall is not due to a rapid breakdown in the body, but occurs because thiopentone is removed rapidly from the plasma and located extensively in a tissue depot (Brodie, 1952)) The nature of this depot is shown by the studies of the distribution of thiopentone in animals (Fig 7) With the exception of muscles and fat, the maximum tissue concentration is reached within one minute of injection and thereafter declines at a rate parallel to the plasma level Equilibrium with the muscles is not attained until a quarter of an hour after injection. The maximum deposition of the drug in adipose tissues occurs within one and a half to two and a half hours of injection in man, but is not complete until about four hours in the dog (Shideman *et al*, 1953). Once a state of equilibrium has been reached, thiopentone appears to be removed slightly faster from fat than from other tissues (Fig 8)

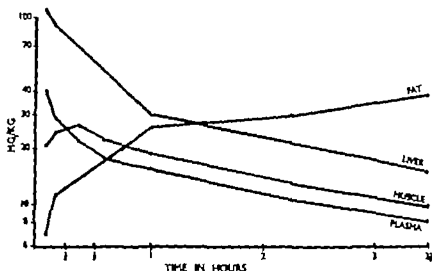


FIG 7.—Concentration of thiopentone in various tissues of the dog after the intravenous administration of 25 mg./kg.
(Brodie, Bernstein and Mark, 1952)

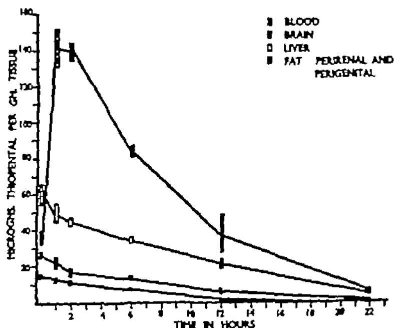


FIG. 8.—Tissue distribution of thiopentone in the rat following the intravenous administration of 30 mg./kg. Curves are drawn through the mean values obtained from 4-6 animals.
(Shideman, Gould, Winters, Peterson and Wilner 1953)

(Thiopentone rapidly crosses the blood brain barrier, and the concentration of the drug in the cerebrospinal fluid reaches a level almost as high as that of the unbound drug in the plasma) There after it declines as in other tissues, the ratio of the plasma to the brain content of the drug being the same half a minute after injection as it is three hours later (Mark, Burns, Campomanes Ngai, Trusof, Papper and Brodie, 1955) Despite earlier suggestions to the contrary the above workers and Brodie, Bernstein and Mark (1952) did not find any selective localisation of the drug in different parts of the nervous system

(Two hours after the administration of large doses of thiopentone in man, by which time diffusion is fairly complete, the decline in plasma concentration is only 10 to 15 per cent. per hour) (Fig 9).

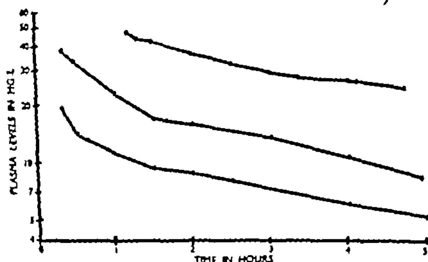


FIG. 9.—Plasma levels of thiopentone after the intravenous administration of 1, 2 and 3 8 g. (lower middle and uper curves respectively) The two smaller doses were given in 5 mins. and the larger one over a 50-minute period.
(Brodie *et al.*, 1950)

This would appear to represent the drug a true rate of metabolic transformation which is thus very slow Shideman has placed this figure at 10 per cent. per hour in the rat. Results from *in vitro* studies by Gould and Shideman (1952) suggest that at high concentrations of thiopentone a constant amount of the drug is detoxicated per unit time, whereas at lower concentrations a constant percentage of the drug present is broken down per unit time.

Brodie (1952) regards thiopentone as being distributed in vivo between two immiscible phases one (mainly a water phase) consists of blood and parenchymatous tissues and the other (the organic phase) is fat.

The relative concentration of undissociated acid largely determines the distribution of a weak organic acid like 5-ethyl 5-(1 methyl butyl)-2 thiobarbituric acid between an aqueous buffer and an immiscible organic solvent. Changes in the *p*H of the aqueous phase will alter the concentration of undissociated acid and thus alter the partition of the drug between the two phases the lower the *p*H the more drug will be in the organic phase, while at a higher *p*H the opposite is true. Decreasing the *p*H of the plasma to 6·8 in dogs by the inhalation of 10 per cent. CO_2 reduced the concentration of thiopentone in the plasma by about 40 per cent. (Table IX) When the inhalation is stopped and the

TABLE IX

Effect of pH *changes on plasma thiopentone levels Average readings for 4 dogs Dogs received 50 to 90 mg /kg thiopentone intravenously After 2 to 2½ hrs., inhalation of* 10 *per cent. carbon dioxide was instituted*

(Calculated from data taken from Brodie *et al.* 1950)

Procedure	*Blood* pH	*Plasma Thiopentone mg /l.*
Control	7·36	33·4
During CO_2 inhalation	6·89	20·8
Recovery	7·33	29·0
Amount of decline (during CO_2 inhalation)	0·47	12·6 (37·8 per cent.)

blood *p*H is returned to near that of the control period, the plasma level of the drug rose sharply The fall in plasma concentration of thiopentone during acidosis must represent a transfer of the drug from plasma to tissues, presumably fatty tissues.

The plasma proteins, especially albumin, are known to bind large numbers of small organic molecules and inorganic ions. The binding of thiopentone and other barbiturates has been studied by Goldbaum and Smith (1948 1950 and 1954). Using ultrafiltration methods, they found a gradual increase in the bound fraction with lengthening of the substituted alkyl side chains.

Thiobarbiturates are bound to a greater extent than their oxygen analogues. Their estimate of the amount of binding of 0·001 Molar thiopentone by 1 per cent. bovine serum albumin in M/15 phosphate buffer at *p*H 7·4 was 65 per cent. Figures for some other barbiturates were: barbitone 5, thiobarbitone 37, pentobarbitone 37 and quinalbarbitone 44.

The degree of binding of all barbiturates varies with the *p*H passing through a maximum at about *p*H 8·0. Increasing the concentration of *p*H 7·4 buffer also caused an increase in the degree of binding of thiopentone. With increasing barbiturate concentration, the percentage of the bound drug diminished although the total amount increased. As the concentration diminished the bound fraction approached unity. At low albumin concentrations, the binding of barbiturates increased rapidly with an increase in albumin until with concentrations of about 3 per cent. further increases in the albumin produced only a small increase in binding.

The strongly bound thiopentone is capable of partially displacing the weaker bound quinalbarbitone or pentobarbitone from their combination with albumin. Goldbaum and Smith suggest that thiobarbiturates are bound partially on the same sites as barbiturates, but not entirely; otherwise one would expect thiopentone, with its greater affinity, to displace almost all of the ordinary barbiturate. Thiopentone, in turn, may be displaced by sodium lauryl sulphonate.

Tissue homogenates bind thiopentone to an extent which cannot be explained on the basis of their plasma content. The extent of the binding to tissues *in vitro* seems to be related to the distribution of the drugs *in vivo*.

Taylor, Richards, Davin and Asher (1954) have also studied the binding of thiopentone with whole plasma, their findings being in fairly close agreement with those of Goldbaum and Smith. They found that plasma from nephrectomised animals bound thiopentone much less than did normal plasma. These workers stress that, unless the degree of binding is known, the thiopentone plasma values are only approximations of the physiologically active concentration in the blood. The concentration in the ultra filtrate is the physiologically active concentration and must be known to interpret pharmacological phenomena. As an example they show that although the plasma content of pento-

barbitone in rabbits at waking (1·16 mg per cent.) is about half of that at which animals awake from thiopentone (2·3 mg per cent.), the active unbound plasma concentrations of the two drugs is about the same on the return of consciousness.

The above conclusions are based on observations of the disposition of thiopentone in the body. The same principles of diffusion, etc. apply to thialbarbitone, thiamylal and hexobarbitone, the plasma concentration time curve for each drug being similar to that for thiopentone (Fig. 10). An early steep fall, indicating

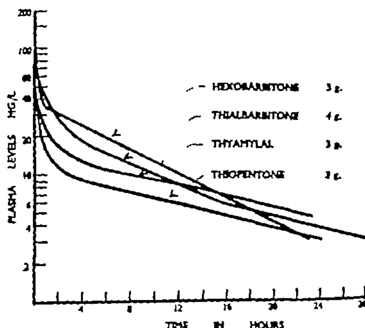


Fig. 10.—Comparison of plasma levels of thiopentone (thiopental), thialbarbitone (Kemithal), thiamylal (Surital) and hexobarbitone (Evipal) in the same man.
(Brodie, 1952)

distribution to non-nervous tissues and fat, is followed by a more gradual decline reflecting the slow rate of metabolic transformation of the drugs. In the subject referred to in Fig. 10 the rate of detoxication of the four drugs was roughly the same, being about 10 per cent. per hour.

It is interesting to compare the distribution of thiopentone in the body with that of its oxygen analogue, pentobarbitone. Brodie (1952) has shown that the two drugs diffuse in a similar manner to all tissues except fat (Table X). Some pentobarbitone

goes into the fat, but not as much as in the case of thiopentone. Fat localisation seems to explain the difference in the duration of

TABLE X

Distribution of pentobarbitone and thiopentone in the dog, 3 hours after intravenous injection of 40 mg/kg

(Brodie 1952)

Tissue	*Ratio* (*Tissue concentration* / *Plasma concentration*)	
	Pentobarbitone	*Thiopentone*
Liver	1·9	1·9
Brain	1·2	1·6
Muscle	0·8	1·5
Kidney	1·4	1·2
Lung	0·6	0·9
Spleen	1·2	0·9
Fat	1·1	6·2

action of the two drugs since the plasma level, which governs the depth of narcosis, remains high with pentobarbitone for a longer period of time. The slower onset of narcosis with this drug as compared with thiopentone, is supposedly due to the fact that barbiturates pass into the brain more slowly than their thio-analogues (Mark *et al.* 1955).

Clinical Observations. After a moderate dose of thiobarbiturate (e.g. 200 to 400 mg thiopentone) the plasma level falls rapidly and the patient quickly recovers. With larger doses, even when equilibrium with the liver, kidney muscles, etc., is complete, the plasma level will still be above that which produces unconsciousness. Removal of the drug from the blood stream now depends on the slower diffusion to fat and on detoxication so that the period of narcosis is increased out of proportion to the increase in dosage. Very large doses may be sufficient to saturate the fat depots completely and there may be a great delay in the return of consciousness. These statements apply in general to fit subjects, but there are many factors to be discussed in more detail later, which alter the normal response to thiopentone.

When a constant level of narcosis is maintained by an infusion of a dilute solution of thiopentone or by intermittent injection of small doses the effects of the diffusion of the drug to non nervous

tissues and fat on the dosage can be observed (Fig. 11). Requirements decrease sharply for about 15 minutes after induction and more slowly thereafter for a further 90 to 120 minutes. When the

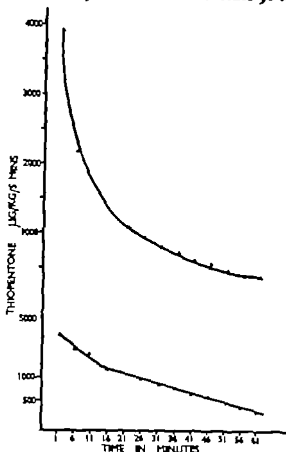


FIG. 11.—Average requirements of thiopentone, in μg./kg./5 mins., required to maintain anaesthesia at a constant depth in 21 normal subjects. In the upper graph the doses are plotted on a linear scale and in the lower on a logarithmic scale. (Dundee, 1955)

maximum concentration of the drug in the body fat has been attained, a constant small dose of thiopentone per unit of time will suffice to maintain sleep. This replaces that removed from the body by detoxication.

The effects of variations in the plasma *p*H can also be detected clinically. The author (1952a) has shown that a rise in *p*H, resulting from slight hyperventilation, decreased the average amount of thiopentone required to maintain anaesthesia, as compared with average doses in subjects with a normal or slightly lowered *p*H (Fig. 12). With prolonged intermittent or continuous administration of thiopentone a constant rate of utilisation of the drug is not reached until about 135 minutes after induction when the respiration is controlled, as compared with 90 to 120 minutes

where respiratory excursion is normal or slightly reduced. This can be attributed to the rise in *p*H prolonging the time taken for complete saturation of the fat depots (Dundee, 1955a)

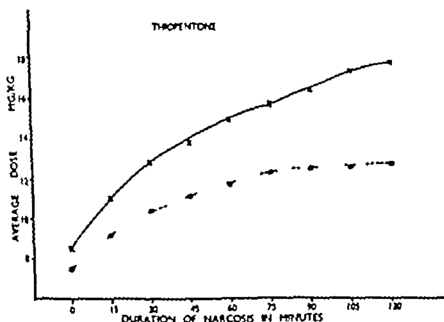


FIG. 12.—Average requirements of thiopentone in two comparable series of 100 cases undergoing abdominal operations under thiopentone-tubocurarine-nitrous oxide-oxygen anaesthesia.

x———x lowered or normal blood *p*H due to slight respiratory depression.

o———o raised blood *p*H resulting from slight over ventilation.

(Dundee, 1955a)

Cumulative Effects. The slow removal of thiopentone from the body leads to a cumulative action when a dose is repeated within 30 hours of a previous injection (Table XI). The prolongation of narcosis at the second injection is particularly marked if the interval between the administration is 6 hours or less Fig. 13 shows that equipotent doses of thiopentone, thialbarbitone and thioethamyl behave in a similar manner in the rat. Thiamylal, on the other hand, does not produce a cumulative effect for a period of longer than 12 hours

Wyngaarden *et al* (1949), who first demonstrated this difference between thiopentone and thiamylal attributed it to the greater potency of the latter The findings of the author (1955b) do not substantiate this view since when equal doses of the two drugs were administered thiamylal was still less cumulative than thio-

TABLE XI

The degree of cumulative action of thiopentone when identical doses were given at the time intervals shown. Figures in brackets show the number of observations of which the average was taken. Doses in man were 8 to 10 mg/kg and in dogs 15 to 20 mg/kg

(Dundee, 1955a)

Time between Administration (hrs.)	Average Duration of the Second Narcosis expressed as a Percentage of the First	
	Humans	Dogs
0–2	1160 (2)	—
2–4	585 (6)	553 (2)
5–7	340 (2)	357 (2)
6–8	—	215 (3)
11–13	—	140 (2)
17–19	—	163 (2)
23–25	158 (2)	132 (2)
29–31	—	100
35–37	—	94
47–49	105 (4)	102 (3)
59–61	—	97 (2)
71–73	87 (2)	102 (4)

pentone. This may be due to a more rapid rate of detoxication of thiamylal and is in keeping with clinical reports in which the action of the two thiobarbiturates is compared. These suggest that there is a more rapid recovery from an equal depth of anaesthesia with thiamylal than with thiopentone.

Swanson and Chen (1953) have shown that the substitution of a CH_3 radical in the 3 position produces thiobarbiturates that have less cumulative effects than either thiopentone or thiamylal. The results of injections of one-half of the AD_{50} to dogs at hourly intervals is shown in Fig 14. Compounds I–IV are CH_3 substituted thiobarbiturates (I is N methyl thiopentone and III is N methyl thiamylal) while V is thiamylal and VI is thiopentone.

FATE IN THE BODY

Thiopentone is almost completely metabolised in man, only about 0·3 per cent. of an administered dose being excreted unchanged in the urine (Brodie, 1952). Carrington and Raventós

(1946) studied the excretion of thialbarbitone in the rabbit and found that about 2·15 per cent. was excreted in the urine in an unchanged form.

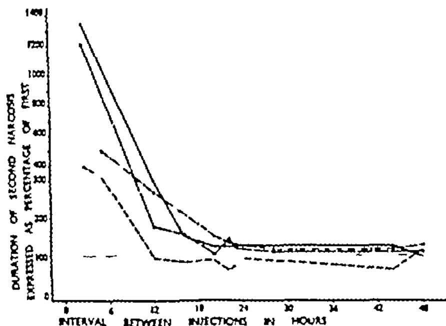


FIG. 13.—Comparison of the cumulative action of equipotent doses of four thiobarbiturates in the rat.

————	thiopentone	(40 mg./kg.)
—— ——	thialbarbitone	(80 mg./kg.)
— — —	thioethamyl	(70 mg./kg.)
— — — —	thiamylal	(34 mg./kg.)

(Dundee 1955b)

Taylor Richards and Tabern (1950 1952) introduced ^{35}S into the molecule of thiopentone and studied the disposal of the radioactive sulphur in various species. Their degree of recovery of this element was as follows

Rat. 40 mg./kg. given by single intraperitoneal injection.
24 hours later—65% radioactivity accounted for in urine.
4 days later —78% " "
— 5% " " " faeces.
— 2% " carcase.

Monkey 35 mg./kg. given intravenously
75% radioactivity accounted for in the urine in the first 24 hours.
85% radioactivity accounted for in the urine in the first 4 days.

These results show that the sulphur containing breakdown

products of thiopentone are mainly excreted in the urine. More than half of the administered dose can be accounted for within the first 24 hours after injection, but its complete removal is very slow

There are several chemical reactions which may be involved in

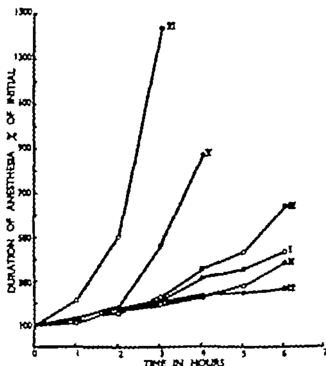


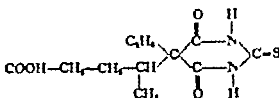
FIG. 14.—Comparison of the cumulative action of six thiobarbiturates. (Swanson and Chen, 1953)

the metabolic fate of barbiturates. Raventós (1954) has classified these as follows

1 Oxidation of radicals in position 5 with the formation of keto hydroxy and carboxy barbiturate radicals.
2. Loss of N-alkyl radicals
3 Desulphuration of thiobarbiturates.
4. Hydrolytic opening of the barbiturate ring

1 Brodie *et al.* (1950) isolated a metabolite, identified as a carboxylic acid derivative of thiopentone, from the urine of men who received large doses of thiopentone. The amounts recovered accounted for 10 to 25 per cent. of the dose of thiopentone ad ministered. In their original paper the authors were not sure of

the position of the carboxylic group of the metabolite, but Woods and Horning (1953) have demonstrated that it is 5 ethyl 5'(4 carboxyl 1 methylbutyl)-2 thiobarbituric acid



Raventós (1954) has reported studies in rabbits on the fate of thialbarbitone. He has been able to isolate from the urine of these animals a thiobarbiturate that contains one more oxygen atom than the administered compound The exact location of this extra oxygen atom in the molecule has not been determined but by analogy with hexobarbitone and cyclobarbitone he suggested that the metabolite is the cyclohexenyl derivative of thialbarbitone.

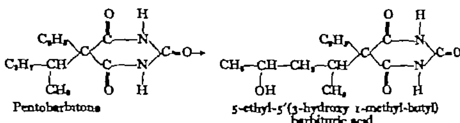
2. The loss of N-alkyl radicals does not apply to any of the thiobarbiturates in common use. It is a possible method of breakdown of the N substituted thiobarbiturates described by Swanson and Chen (1953) This additional method of detoxication may account for the shorter period of narcosis and less cumulative action that occurs with these drugs as compared with thiopentone and thiamylal (Fig 14)

Demethylation plays a part in the breakdown of hexobarbitone. Bush Butler and Dickinson (1953) have found that about 25 per cent. of the administered drug is demethylated in the body

3 The finding of inorganic and ethereal ^{35}S sulphates by Taylor and his colleagues in the urine of animals injected with radioactive thiopentone shows that thiobarbiturates can lose their sulphur atoms and be transformed into barbiturates. The demonstration of ^{35}S in the carcase of the experimental animals four days after the administration of radioactive thiopentone suggests that some of its sulphur may be used in the normal metabolism of the animals in the formation of sulphur containing amino acids and proteins.

Since Carrington and Raventós (1946) were only able to detect about 2·7 per cent. of 5 allyl 5'-cyclohexenyl-barbituric acid in the urine of rabbits injected with thialbarbitone, it would seem that desulphuration of thiobarbiturates does not play a very important part in their metabolism. The barbiturates so formed follow the normal metabolic fate of these substances. As an example,

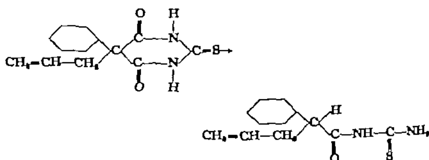
desulphuration of thiopentone leads to the formation of pentobarbitone. Maynert and Van Dyke (1949) and Brodie, Burns, Mark, Lief Bernstein and Papper (1953) have demonstrated oxidation of its side chain as follows



Pentobarbitone — 5-ethyl-5'(3-hydroxy 1-methyl-butyl) barbituric acid

4. Scholne *et al.* (1933) suggested that, because of the small amounts of drug found in the urine after the administration of medium acting barbiturates, inactivation of these compounds involved the rupture of the barbituric acid ring. Van Dyke, Scudi and Tabern (1947) showed that this did not play a part in the detoxication of pentobarbitone. After the administration of pentobarbitone labelled with ^{15}N they found less than 8 per cent. of the isotope was excreted as ammonia and urea. Taylor *et al.* (1950) in animals injected with ^{35}S thiopentone found that the amount of ^{35}S thiourea in the urine during the first 24 hours accounted for only 2 to 8 per cent. of the administered thiopentone.

Raventós (1954) has demonstrated that the urine of rabbits injected with thialbarbitone contains amounts of thiourea which represents 0·5 to 2·0 per cent. of the dose. He has obtained a neutral sulphur-containing fraction having the same ultra violet spectrum as the thiourea derivative of thialbarbitone.



While there is no doubt that hydrolytic opening of the barbituric

ring structure does occur, it appears to play a minor role in the breakdown of thiobarbiturates in the body

Site of Detoxication Prior to 1940 it was assumed that thiopentone was destroyed primarily by the liver This assumption may have been based on the observation, first made by Pratt in 1933 and later confirmed by many workers that its oxygen analogue (pentobarbitone) is broken down in the liver Hexobarbitone, its immediate predecessor in intravenous anaesthesia, was also shown by Cameron and de Saram (1939) to be metabolised in the liver

Scheifley and Higgins (1940) verified *that hepatic dysfunction produced by partial hepatectomy* prolonged the action of pentobarbitone narcosis in the rat, but found that it had no significant effect on thiopentone narcosis. This latter finding was verified by Mason and Beland in 1945 Richards and Appel (1941) were unable to detect any appreciable difference in sleeping time with thiopentone in rats before and after the production of liver damage by carbon tetrachloride. Fatty infiltration of the liver, as the results of prolonged feeding on a choline-free diet, likewise had no effect on the duration of thiopentone narcosis in the rat.

The above work led to the suggestions from many sources that thiopentone was detoxicated equally by all body tissues. The first evidence to the contrary came from Shideman Kelly and Adams (1947) in their reports on the effect of liver dysfunction, produced by three methods, on the duration of narcosis with thiopentone, thiamylal and thioethamyl. The results of their experiments carried out in mice and rats are shown in Table XII These reveal a consistent prolongation of sleep with each of the three thiobarbiturates in the presence of hepatic damage, thus again focusing attention on the liver as the main site of detoxication of these drugs.

The divergence of results of Shideman *et al* from previous works was explained *by the former on the grounds that* restoration of the liver following partial hepatectomy begins about 24 hours after surgery and the remaining remnant more than doubles itself in 72 hours. Scheifley and Higgins removed only 70 per cent. of the liver and allowed considerable regeneration to occur before proceeding with the experiment, whereas Shideman and his co-workers performed an 85 to 90 per cent. hepatectomy, the thiobarbiturates being injected 24 hours after this procedure

TABLE XII

Effect of hepatic dysfunction produced by various means on the duration of action of three thiobarbiturates

(Shideman *et al.*, 1947)

Drug	Group	Number of Animals	Duration of Action (min.)		Difference of Means		
			First Injection	Second Injection	Min	Per cent.	Value of Difference
1 Thiopentone 58 mg./kg. I V	A	22	12·3	13·5	+ 1·2	+ 9·7	0·797
	B	21	14·5	184·0	+169·5	+1169·0	3·41
Thiamylal 45 mg./kg. I V	A	25	22·4	25·6	+ 3·2	+ 14·3	1·77
	B	29	19·2	149·2	+130·0	+ 676·0	4·52
Thioethamyl 80 mg./kg I.V	A	24	10·6	7·2	− 3·4	− 32·1	3·03
	B	23	9·5	234·1	+224·6	+2364·0	2·75
2. Thiopentone 30 mg./kg I.V	C	12	34·4	31·0	− 3·4	− 9·8	0·631
	D	10	23·8	219·5	+195·7	+ 822·0	2·39
			Mean Duration (Min.)				
3 Thiopentone 30 mg./kg. I V	E	15	26·4		+198·2	+ 751·0	7·76
	F	9	224·6				
Thiamylal 20 mg./kg. I V	E	15	7·0		+ 17·4	+ 249·0	3·32
	F	15	24·4				
Thiamylal 25 mg./kg. I.V	E	13	35·7		+154·4	+ 432·0	3·16
	F	9	190·1				
Thioethamyl 50 mg. /kg I V	E	21	27·3		+ 84·4	+ 309·0	3·25
	F	17	111·7				

1 *Carbon tetrachloride* (mice). Second injection given 4 days after first.
A. Controls. B. Liver dysfunction produced 24 hours previously

2. *Partial hepatectomy* (rats). Second injection given 1 week after first.
C. Controls. D 85 to 90% of the liver removed 24 hours prior to second injection

A further criticism of Mason and Beland's work was their assumption that absorption of thiopentone from a severely traumatised peritoneal cavity, such as follows an operation on the liver, is the same as from a normal animal. The absence of statistical analysis of the data of Richards and Appel is given as a reason for doubting the validity of their findings. Another explanation for the discrepancy in results may be that recovery from the thiopentone was achieved in some of the series solely by diffusion of the drug to non nervous tissues.

Subsequent work by Walker and Wynn Parry (1949) confirmed that partial hepatectomy prolonged the action of thiopentone in the rat. They also showed that as liver regeneration occurs, so does the duration of narcosis return to normal (Table XIII).

TABLE XIII

Differences in mean sleeping time of groups of rats after 50 mg/kg thiopentone on various days after partial hepatectomy

(Walker and Wynn Parry 1949)

Number of Rats	*Days after Hepatectomy*	*Mean Sleeping-time (min.) before Hepatectomy*	*Mean Sleeping-time (min.) after Hepatectomy**	*Difference*
3	4	133·3	573·3 (2)	+440·0
10	8	94·1	314·0 (3)	+219·0
8	12	12·0	227·0 (2)	+215·0
10	15	86·8	212·4 (1)	+125·6
8	20	92·0	110·0 (1)	+ 18·0

* Numbers in brackets refer to deaths due to the effect of the drug after hepatectomy. These deaths are included in figures each as 500 min. sleeping-time.

Meyers and Peoples (1954) eliminated liver function in dogs by ligation of the portal vein and hepatic artery after an Eck fistula had been established. When this procedure was carried out under thiopentone anaesthesia, the animals did not show signs of wakening during a period of at least four times that necessary for sham operated animals to recover.

As regards the effect of hepatic dysfunction on the duration of narcosis, thialbarbitone has not been studied to the same extent as other thiobarbiturates. Binda and Rollino (1951) found that ligation of the hepatic arteries in the dog did not result in a pro-

longation of action of the drug. He inferred from the results that the liver is not essential for its rapid elimination. The degree of liver dysfunction produced is not stated, and there is no evidence to show that with the dosage used the animals would not recover from the thialbarbitone by diffusion of the drug to non-nervous tissues

The author has investigated the effect of liver dysfunction on the duration of action of thiabarbitone in the rat. The experiment was somewhat similar to those described by Shideman *et al.* (1947) for other thiobarbiturates.

Male rats of the Wistar strain were used. Two control readings were made at 5-day intervals, and after each estimation 4 rats were killed and the serum cholinesterase estimated. This quantity was used as an index of the liver function. CCl_4 was used to produce liver damage. There was a high mortality following the CCl_4 and the survivors were divided into two batches thialbarbitone was injected 24 hours later in the first group and 48 hours later to the second group. In order to maintain the number of survivors, serum cholinesterase estimations were done at this stage only on those rats which died under anaesthesia.

The results (Table XIV) show that thialbarbitone behaves in a similar fashion to thiopentone and thiamylal. A significant increase in narcosis occurred on the first and second days after the injection of carbon tetrachloride, sleeping-time returning to normal on the tenth day Serum cholinesterase was unchanged until the second day after the production of liver dysfunction, when it was reduced by 50 per cent. returning to normal on the tenth day The findings suggest that the liver plays the same part in the detoxication of thialbarbitone as it does with other thiobarbiturates.

In man controlled observations on the effect of liver dysfunction on thiobarbiturate narcosis are few Shideman, Kelly Lee, Lowell and Adams (1949) have compared the sleeping time after 4 mg /kg thiopentone in subjects with normal and abnormal liver function (Table XV). The duration of narcosis was significantly longer in patients with liver damage as compared with normal subjects of approximately the same age. To exclude the natural variation in response of different subjects to thiopentone the author (1952b) has compared the duration of action of the same dose in the same persons before and after the production of liver dysfunction in patients who had previously had a chloroform anaesthetic for some

TABLE XIV

The effect of liver dysfunction produced by carbon tetrachloride on the duration of thialbarbitone narcosis in the rat

Days	Procedure	No. of Rats	% Anaesthetised	% Mortality	Average Duration of Narcosis (mins.)	Serum Chol. esterase µl./CO_2/ml. blood/hour: Average	Serum Chol. esterase µl./CO_2/ml. blood/hour: No. of Estimations
1	Thialbarbitone (70 mg./kg. I.P.)	50	88	2	22·9 ± 2·2	220	4
6	Thialbarbitone (70 mg./kg. I.P.)	45	85	2·2	24·2 ± 2·2	217	4
13	Carbon tetrachloride (0·5 ml. 50% solution I.M.)	40		40			
14	Thialbarbitone (70 mg./kg. I.P.)	12	92·5	42·5	63·5 ± 3·2	198	4
15	Thialbarbitone (70 mg./kg. I.P.)	12	100	16·7	44·0 ± 8·3	122	4
23	Thialbarbitone (70 mg./kg. I.P.)	16	75	0	18·1 ± 6·2	210	8

D

TABLE XVII

Distribution of thiopentone (25 mg./kg. I.V.) in tissues of rabbi[ts] before and 24 hours after nephrectomy

(Richards, Taylor and Kueter 1953)

	Controls	*Nephrectomised*
Sleeping-time (mins.)	24±3·8	31±16
Average time sample taken	64	54
Plasma	11·6±3·1 mg./kg.	16·1±2·6 mg./kg.
Muscle	11·3±4·0 mg./kg.	14·4±3·9 mg./kg.
Fat	51·9±29 mg./kg.	88·3±21 mg./kg.

Fig. 15 shows that the liver plays a greater part than the kidne[y] in the breakdown of thiopentone *in vivo*.

The *in vitro* studies reported to date are in close agreeme[nt] with the above. Shideman *et al.* (1947) found that thiopento[ne]

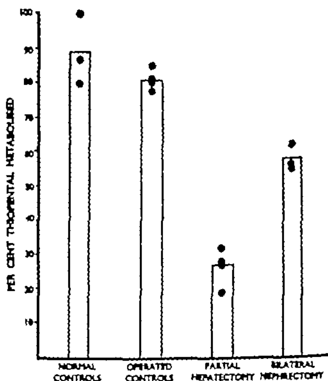


FIG. 15.—Effect of partial hepatectomy and bilateral nephrectomy on the *in vivo* rate of metabolism of thiopentone.
(Shideman *et al.*, 1953)

incubated with liver slices for one hour underwent 12 6 to 14 5 per cent. inactivation 16·9 to 37 per cent. was broken down in three hours and 40 to 75 per cent after four hours Similar results were found with liver mince Heat inactivated liver showed little ability to degrade thiopentone. Liver, kidney, muscle and brain were all used in similar incubation experiments by Dorfman and Goldbaum (1947) Rabbit liver slices inactivated thiopentone liver brei showed somewhat less activity while homogenised liver had no activity Kidney slices had a similar action to liver slices, brain showed very slight activity and muscle had none.

Kelly and Shideman (1949) compared the plasma decay curves in the heart lung heart lung liver and heart lung kidney prepara tion of the dog The heart lung preparation showed a very gradually falling thiopentone level about one-quarter of the drug having disappeared after 70 minutes. Over the same time two and a half times that quantity was removed by the heart lung liver preparation The heart lung kidney degraded thiopentone, but not nearly as rapidly as the heart lung liver preparation.

Richards (1947) found that incubation of thiopentone with whole blood at 37° C. significantly reduces the potency of the barbiturates. Plasma is inactive in this respect. If the incubated mixture is administered intravenously a decrease in the expected duration of narcosis will result, but with intraperitoneal injection this does not occur This suggests that, rather than the blood breaking down the thiopentone an erythrocyte-thiopentone linkage occurs. Only the non linked thiopentone will act after intravenous injection but this linkage is broken down when all the drug is released in the peritoneal cavity

The enzymes used by the tissues in the metabolic transformation of thiopentone have been studied by Gould and Shideman (1952) They described a cell free homogenate of rat liver which is capable of detoxicating the drug (Table XVIII) Its optimum *p*H was between 6 4 and 9 4. For maximum activity of this preparation cytochrome c, adenosine triphosphate, nicotinamide and a substrate are necessary Of those substrates employed, Krebs cycle intermediates (citrate, ketoglutartrate, succinate, formate, malonate) function best. The exclusion of nicotinamide results in the most striking decrease in metabolism. An increase in the amount of liver in the incubating medium results in an increase in the total amount of thiopentone metabolised, but

to two minutes and the usual signs and stages of anaesthesia cannot be detected.) However, it has been shown by Etsten and Himwich (1946), who studied the effects of thiopentone when given slowly in a 1 per cent. solution, that the pattern of depression of the

TABLE XIX

Demonstration of acute tolerance of thiopentone in man

(Brodie, 1952)

The plasma concentrations at the time of orientation following the small doses are lower than the corresponding levels following the larger doses by an average of 8·6 mg./l. Despite the small number of observations, this difference is statistically highly significant ($p<0{\cdot}01$).

		Plasma Levels and Concurrent Signs of Anaesthesia		
Subject	*Dose of Thiopentone*	*Conjunctival Reflex*	*Eyeball Motion*	*Orientation (Awakening)*
	mg./kg	mg./l.	mg./l.	mg./l.
V	59	—	32·6	32·6
	36	24·3	22·6	22·6
M	67	27·8	27·8	27·8
	40	19·3	19·3	19·3
G	43	22·8	—	19·8
	22	14·6	—	13·2
N	50	27	26·7	26·0
	54	25·8	24·9	24·9
	65	31·6	—	27·0
	33	16·8	16·8	16·8

central nervous system is similar in many respects to that seen with other anaesthetic agents. They have classified the stages of thiopentone narcosis and correlated their observations with depression of different parts of the brain (Fig. 16). Their concept of progressive depression of the central nervous system is based on the suggestion, first made by Hughlings Jackson in 1884, that the *new phylogenetic* and *higher functional portions* of the brain regulate and control the older and lower areas. When function is depressed in a newer layer the part immediately below assumes dominant control. Because of the unreliability of the usual signs of anaesthesia as an indication of the depth of narcosis with thiopentone, the suggested stages of Etsten and Himwich will not be discussed in detail.

STAGE	ANESTHESIA	CHARACTERISTICS	SITE of DEPRESSION	BRAIN
I	CLOUDING	EUPHORIA LOSS of DISCRIMINATION TO IMPAIRMENT of ENVIRONMENTAL CONTACT	SLIGHT DEPRESSION of CORTEX TO MODERATE DEPRESSION of CORTEX	
II	HYPER SENSITIVITY	LOSS of CONSCIOUSNESS	PREDOMINANT CONTROL by SUBCORTEX	
III Plane I	LIGHT SURGICAL	HYPOACTIVITY to PAINFUL STIMULUS	MODERATE DEPRESSION of SUBCORTEX	
Plane II	MODERATE SURGICAL	LOSS of SOMATIC RESPONSE to PAIN	PREDOMINANT CONTROL by MIDBRAIN	
Plane III	DEEP SURGICAL	LOSS of VISCERAL RESPONSE to PAIN	MODERATE DEPRESSION of MIDBRAIN	
IV	IMPENDING FAILURE	FALL in PULSE PRESSURE	MODERATE DEPRESSION of PONS	

Fig. 16.—A correlation between the stages of thiopentone anaesthesia and the outstanding clinical signs and their neuro-anatomical allocations.

(Etsten and Himwich 1946)

The effects of increasing doses of thiopentone on the nervous system are first manifested by a gradual depression of consciousness. Environmental contact and the performance of voluntar, movement are progressively impaired the ability to answer questions is gradually abolished and a state of euphoria invariably occurs before consciousness is lost. Hypersensitivity to touch or pain stimuli may be present just before loss of consciousness and is a constant finding once this has occurred. Concurrently there may also be hyperexcitability of the pharyngeal and laryngeal reflexes. The response evoked by stimuli is at first purposeful, attempting to remove or withdraw from the cause. It later assumes the form of a mass withdrawal reflex which gradually diminishes and is completely abolished in deep anaesthesia.

The eyeball begins to move slightly before consciousness is lost. During the stage of hyperexcitability it may be deviated from the midline, gradually becoming central and remaining so during the deeper planes of anaesthesia. In the absence of stimuli, or large doses of mydriatic drugs the pupil remains small until paralytic or anoxic dilatation occurs in deep narcosis. Reflex dilatation may however occur immediately after the loss of consciousness, but this response is quickly lost as anaesthesia deepens.

Differences from Ether The clinical pattern of depression of the central nervous system by thiobarbiturates differs from the classical picture of ether anaesthesia in several respects. After large doses of thiopentone respiration is progressively depressed until apnoea occurs, sometimes at a depth of anaesthesia which is insufficient to permit surgical intervention. The excitement stage, so characteristic of ether is rarely seen with intravenous agents. Thiobarbiturates have little, if any analgesic effect and reflex responses to stimuli are not abolished until an appreciably greate depth of anaesthesia is reached than is required with ether Th degree of muscular relaxation produced by thiopentone and similar drugs is generally poor

Some of these differences may be explained by the irritant effects of ether on the tracheobronchial tree. This stimulus (which is absent with thiobarbiturates) results in an increased respiratory volume until a deep level of anaesthesia is reached. Its absence may account for the lowered incidence of excitement seen with the intravenous agents. The analgesic properties of ether result in

less stimuli reaching the brain thereby resulting in a suppression of reflex activity at lighter levels of anaesthesia with this agent than with thiobarbiturates. Since relaxation of the abdominal muscles is helped by the elimination of sensory stimuli the failure of moderate doses of thiopentone to suppress these stimuli may contribute to their poor muscle-relaxing properties. Anoxia, resulting from respiratory depression, may be another contributory factor. The differences between the action of thiopentone and ether on the myoneural junctions will be discussed in detail on page 102.

With the thiobarbiturates more so than with any other drugs used in anaesthesia the clinical level of narcosis is related to the intensity of the surgical stimulus. Hence it is impossible to be as dogmatic about the signs and stages of anaesthesia with these drugs as with the ethers. With the latter the agents themselves act as a stimulus and a more consistent pattern of depression occurs. For example, an undisturbed patient who has received 500 mg thiopentone may have depressed respiration and the abdominal and jaw muscles may be quite relaxed, corresponding to the second or third plane of the third stage of anaesthesia with ether (Guedel classification). If a towel clip is applied the respiratory volume increases, relaxation will be lost and there may be reflex movement of a limb. We have now a patient whose depth of anaesthesia would be assessed as second stage or first plane of the third stage.

Because of the lack of analgesic properties the signs and stages of anaesthesia with thiobarbiturates are more affected by premedication with analgesic drugs than is the case with inhalation agents. This also applies to supplementation during anaesthesia with analgesic drugs whether these be of the opiate type or analgesic mixtures of nitrous oxide/oxygen. They reduce or abolish reflex response to stimuli, and enable operative procedures to be carried out at plasma levels of thiopentone which would be insufficient if the drug were given alone (see convulsive properties, p. 70).

Electroencephalographic Changes. Characteristic changes in the electroencephalographic pattern during thiopentone narcosis have been noted by many workers (Brazier *et al.*, 1945; Tucci *et al.*, 1949; Kiersey *et al.*, 1951). With only minor variations there is general agreement on the pattern of these changes

and their relation to the depth of anaesthesia. They have been classified by Kiersey and his colleagues as follows (Fig 17)

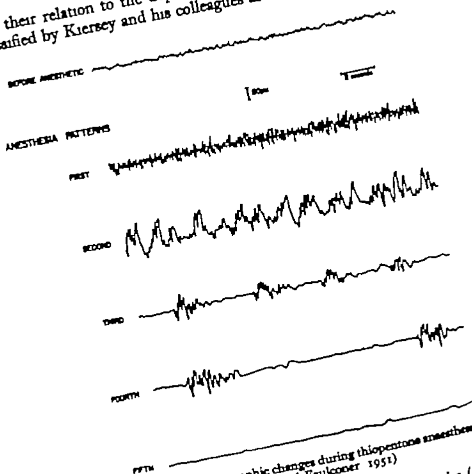


FIG. 17.—Electroencephalographic changes during thiopentone anaesthesia. (Kiersey Bickford and Faulconer 1951)

1 High amplitude, fast spiky activity of mixed frequencies (10 to 30 cycles./sec.), with the predominant frequency near 20 cycles/sec. Amplitudes vary greatly short runs of two, three or more waves with an amplitude of 75 to 80 microvolts are characteristically preceded and followed by similar runs of lower amplitude.

2. Complex pattern of many frequencies differing from the preceding by the presence of predominantly slower wave forms of very irregular contour and random occurrence. There is also much variation in voltage the larger and predominant waves representing close to 150 microvolts. Superimposed on these slower waves and occupying the intervals between them is a much faster activity rather spiky in character and irregular in amplitude. The frequency is about 10 cycles/sec. and the amplitude is comparable with that seen in the first pattern.

3 Characterised by a progressive suppression of cortical activity,

short periods of relative quiescence separating groups or bursts of waves. The bursts are frequently made up of two distinct elements, the first appearing abruptly and consisting of a short series of high voltage waves with a frequency of about 10 cycles/sec. and continuing for about one second. The second element follows immediately in the form of two or more slow waves at a frequency of near 2 cycles/sec. and tailing off into the next suppression phrase. The whole complex occupies a time interval of two or more seconds. In this stage the intervals of quiescence do not exceed three seconds.

4. This differs from the above in that the duration of the periods of cortical inactivity vary from three to ten seconds.

5 Periods of activity do not appear any more frequently than once every ten seconds. There is a reduction in the amplitude of the com ponents which may fall below 25 microvolts.

During the transition from one pattern to another there is usually a mixture of both patterns. This is especially noticeable in the persistence of fast waves in the second pattern. In fact, an activity of ten cycles per second or faster can be followed through into the fifth pattern, where it makes up part of the active elements.

The fast spiky pattern in (1) may appear within one minute of injecting as little as 50 mg thiopentone. Increasing the dosage increases the overall amplitude without altering the frequency during this phase. The patient is still awake and feels drowsy and euphoric. The Harvard School (Finesinger *et al.*, 1947 Tucci *et al.*, 1949) state that the appearance of the slower waves (2) coincides with the loss of consciousness. Kiersey and his co-workers found that the exact moment when a person loses contact with the environment seems to depend on the strength of his efforts to maintain consciousness. They did not find it constantly characterised by any special change in the electroencephalogram and it may even appear before the onset of pattern (2)

In (2) at first the lash reflex is present and there is a brisk withdrawal reflex in response to painful stimulation of the skin. When reflex activity becomes more sluggish, the slower waves predominate and often increase in amplitude. As anaesthesia deepens, the withdrawal reflex is abolished, the corneal reflex disappears and the eyeballs become fixed. There is a slight fall in blood pressure and there may be some respiratory depression The pupils reaction to light remains brisk. When this stage is well established, the majority of patients will tolerate a skin incision or a pharyngeal airway

As the third pattern appears, reduction of respiratory volume

becomes most marked. This respiratory depression increases progressively through (4) and (5), and during the latter it may be necessary to aid the respiration. The light reflex remains active throughout all the stages described.

(In stressing the possible value of the electroencephalogram in assessing the depth of anaesthesia with thiopentone Kiersey *et al.* noted that the use of *d* tubocurarine chloride did not affect the above patterns, provided that the resulting respiratory depression did not result in hypoxia or carbon dioxide retention.)

Cerebral Metabolism and Blood Flow Wechsler, Dripps and Kety (1951) studied the effects of thiopentone on cerebral blood flow in man. Their average findings in 10 subjects (Table XX) compared with normal values, indicate a reduction in cerebral metabolism, even though the quantity of available oxygen is not reduced. This finding had been noted by previous workers, but Etsten, York and Himwich (1946) and Himwich *et al.* (1947) suggested that oxidation was not decreased to the same extent in all parts of the brain at the lighter levels of narcosis. Their conclusions that the cerebrum was affected before the other parts of the brain was based on the findings of a difference in the oxygen content of the two jugular veins. This is not confirmed in Table XX.

TABLE XX

Effects of thiopentone on cerebral metabolism and blood flow
(Wechsler Dripps and Kety 1951)

	Normal	During Thiopentone Narcosis	
		Right	Left
Respiratory Quotient	1	0·87	0·95
Arteriovenous O_2 difference (vols. per cent.)	6·3	3·7	3·6
Cerebral blood flow (ml./100 g./min.)	54·0	60·2	60·8
Cerebral metabolic rate (O_2) (ml./100 g./min.)	3·3	2·1	2·1
Cerebrovascular resistance (mm. Hg. ml./100 g./min.)	1·6	1·3	1·3

The depth of anaesthesia is related to the degree of depression of cerebral oxygen consumption. In seminarcotic doses, sufficient to make schizophrenic patients more accessible, Kety and

his co-workers (1948) found that thiopentone had no effect on the circulation or oxygen consumption of the brain as a whole. Comparing the effect of light and deep thiopentone narcosis on cerebral metabolism in the dog Homburger *et al* (1946) noted a fall from 5·9 to 2·6 ml. oxygen/100 g. brain/min. a decrease of 56 per cent.

Although the mean arterial blood pressure in the patients under thiopentone in Table XX was 71 mm. Hg as compared with 85 mm. Hg in normal subjects, there was an increase in cerebral blood flow. Wechsler *et al.* (1951) attribute this in part to the decreased tone of cerebral vessels—indicated by reduced cerebro-vascular resistance—due to an increased blood content of carbon dioxide as a result of respiratory depression following thiopentone. Wilson Odom and Schieve (1953) could not detect any difference between the cerebral blood flow in 10 patients before and after thiopentone. However, the drug did not prevent the vasodilating effects of carbon dioxide. In another series of 6 patients they observed an increase in cerebrospinal fluid pressure after thiopentone, which was more than doubled by the inhalation of 7 per cent. carbon dioxide. The average dose of thiopentone administered to Wechsler's patients was 930 mg. (range 500 to 1600 mg.) while in the later series doses varied from 200 to 600 mg. These findings suggest that the degree of carbon dioxide retention, as the result of respiratory depression, is the main factor in determining whether cerebral blood flow and cerebrospinal fluid pressure are affected by thiopentone.

Many reports of *in vitro* studies show that effective doses of narcotic reversibly inhibit some of the enzymatic and respiratory processes in cerebral cells. Thiobarbiturates have not received the same attention as other barbiturates in this respect. In view of the relationship between the inhibition of cell respiration and the mode of action of barbiturates in producing narcosis this work will be briefly reviewed.

Quastel (1939) has pointed out that glucose is the principal substrate of the brain in living animals and oxygen utilised by the brain is mainly concerned with the combustion of glucose supplied by the blood. Deprivation of glucose from the brain results in as dire effects as deprivation of oxygen, mental activity depending on maintaining the supply of oxygen and glucose to the central nervous system. Quastel and Wheatley (1932) found a correlation

between the hypnotic powers of several di alkyl barbituric acid derivatives and their ability to inhibit oxygen consumption of minced guinea pig brain. The oxidations of glucose, and its metabolites, lactate and pyruvate were most affected while those of succinate and *p*-phenylene diamine were undisturbed. The respiration of tissues other than the brain was less affected (Table XXI) This is due to the predominant role of carbohydrate

TABLE XXI

Effect of 0·033 per cent hexobarbitone on respiration of guinea pig tissues in the presence of glucose

(Quastel, 1952)

Tissue	*Respiration* ($Q\,O_2$)	*Respiration* ($Q\,O_2$) *in the presence of Narcotic*	*% Inhibition by Narcotic*
Brain	14·2	9·5	33
Spleen	7·7	6·4	17
Liver	4·25	4·15	2
Testis	8·65	7·25	16
Kidney	15·2	15·95	nil

metabolism in the brain, which is therefore more sensitive to narcotics than other tissues.

A study of the various links leading to the oxidation of glucose revealed that only one part of the chain is affected by narcotics (Table XXII) This has been confirmed by Greig (1946), who

TABLE XXII

Narcotic sensitive respiratory system

(Quastel, 1952)

Substrate—Dehydrogenase—Coxymase—Flavoprotein—Cytochrome

Narcotic Insensitive Region | *Narcotic Sensitive Region*

—Cytochrome—Oxygen Oxidase

Narcotic Insensitive Region

postulated that, in the presence of narcotics there is a binding of reduced flavoprotein and cytochrome 'b'

Potassium is essential for the effects of narcotics on cells, being required as a catalyst in the interaction of pyruvate and adenosinetriphosphate. The formation of adenosinetriphosphate is essential for the activity of cells and for the synthesis of acetyl choline. In the presence of quantities of narcotics which suppress cellular respiration, the formation of acetylcholine by the brain is also decreased [Quastel (1952) suggests that the major effect of narcotics on the brain is not merely to reduce the oxygen requirements by cerebral cells, but to impede a step, largely concerned with adenosinetriphosphate synthesis in the sequence of events leading to complete oxidation of glucose.]

(It is known that acetylcholine is present in the brain in a bound form. With low concentrations of narcotics—insufficient to have any marked effect on cellular respiration or adenosinetriphosphate synthesis—there is a release of free acetylcholine from the bound form. The excitant effects of acetylcholine on brain potentials may explain the stimulant effects of small doses of thiopentone detected on the electroencephalogram by Tucci *et al* (1949) It also offers an explanation for the excitement during the induction of anaesthesia, other than the classical ' release of cortical inhibition With larger doses of thiopentone there is a depression of acetylcholine synthesis, or other synthesis dependent on adenosinetriphosphate formation, with consequent inability of the affected cells to maintain their normal function.)

Sodium Succinate. The work of Quastel and Wheatley (1932) has shown that barbiturates decrease oxygen consumption of brain slices *in vitro* by inhibiting the oxidation of glucose, lactate and pyruvate. The oxidation of succinate is unaffected. It was suggested by Soskin and Taubenhaus (1943) that supplying sufficient of the latter substrate might adequately maintain the metabolism of the brain following an overdose of barbiturate. They found that sodium succinate shortened pentobarbitone and amylobarbitone narcosis in rats.

Barrett (1947, 1948) extended this concept and found that disodium succinate hexahydrate, given either intermittently as 30 per cent. solution intravenously or in a 10 per cent. drip form shortened the duration of thiopentone narcosis in man. Tucci *et al.* (1949) studied the effects of thiopentone and succinate on

between the hypnotic powers of several di alkyl barbituric and derivatives and their ability to inhibit oxygen consumption of minced guinea pig brain. The oxidations of glucose, and its metabolites, lactate and pyruvate were most affected while those of succinate and *p*-phenylene diamine were undisturbed. The respiration of tissues other than the brain was less affected (Table XXI) This is due to the predominant role of carbohydrate

TABLE XXI

Effect of 0·033 per cent hexobarbitone on respiration of guinea pig tissues in the presence of glucose

(Quastel, 1952)

Tissue	Respiration (QO_2)	Respiration (QO_2) in the presence of Narcotic	% Inhibition by Narcotic
Brain	14·2	9·5	33
Spleen	7·7	6·4	17
Liver	4·25	4·15	2
Testis	8·65	7·25	16
Kidney	15·2	15·95	nil

metabolism in the brain, which is therefore more sensitive to narcotics than other tissues.

A study of the various links leading to the oxidation of glucose revealed that only one part of the chain is affected by narcotics (Table XXII) This has been confirmed by Greig (1946), who

TABLE XXII

Narcotic sensitive respiratory system

(Quastel, 1952)

Substrate—Dehydrogenase—Coenzyme—Flavoprotein—Cytochrome

Narcotic Insensitive Region *Narcotic Sensitive Region*

—Cytochrome—Oxygen Oxidase

Narcotic Insensitive Region

postulated that, in the presence of narcotics, there is a binding of reduced flavoprotein and cytochrome "b"

Potassium is essential for the effects of narcotics on cells being required as a catalyst in the interaction of pyruvate and adenosinetriphosphate. The formation of adenosinetriphosphate is essential for the activity of cells and for the synthesis of acetyl choline. In the presence of quantities of narcotics which suppress cellular respiration, the formation of acetylcholine by the brain is also decreased [Quastel (1952) suggests that the major effect of narcotics on the brain is not merely to reduce the oxygen requirements by cerebral cells, but to impede a step, largely concerned with adenosinetriphosphate synthesis in the sequence of events leading to complete oxidation of glucose.]

(It is known that acetylcholine is present in the brain in a bound form With low concentrations of narcotics—insufficient to have any marked effect on cellular respiration or adenosinetriphosphate synthesis—there is a release of free acetylcholine from the bound form. The excitant effects of acetylcholine on brain potentials may explain the stimulant effects of small doses of thiopentone detected on the electroencephalogram by Tucci *et al.* (1949) It also offers an explanation for the excitement during the induction of anaesthesia, other than the classical "release of cortical inhibition" With larger doses of thiopentone there is a depression of acetylcholine synthesis, or other synthesis dependent on adenosinetriphosphate formation, with consequent inability of the affected cells to maintain their normal function.)

Sodium Succinate. The work of Quastel and Wheatley (1932) has shown that barbiturates decrease oxygen consumption of brain slices *in vitro* by inhibiting the oxidation of glucose, lactate and pyruvate. The oxidation of succinate is unaffected. It was suggested by Soskin and Taubenhaus (1943) that supplying sufficient of the latter substrate might adequately maintain the metabolism of the brain following an overdose of barbiturate. They found that sodium succinate shortened pentobarbitone and amylobarbitone narcosis in rats

Barrett (1947, 1948) extended this concept and found that disodium succinate hexahydrate, given either intermittently as 30 per cent. solution intravenously or in a 10 per cent. drip form shortened the duration of thiopentone narcosis in man. Tucci *et al.* (1949) studied the effects of thiopentone and succinate on

the electroencephalogram tracings in man and found variable results. As the result of a well-planned investigation, Vanderwater and Gordon (1952) concluded that sodium succinate produces no significant change in the waking time of human subjects after thiopentone. Zoboli (1951) while agreeing with the above workers, thought that the drug might have some slight value as a respiratory stimulant.

More recent work in this field by Giarman, Rowe and Young (1954) has included a study of the analeptic effect in mice of ethyl succinate and bis-dimethylaminoethyl succinate as well as sodium succinate. No antagonism to thiopentone was observed, but rather the opposite, as in certain doses all three succinate derivatives significantly prolonged the anaesthesia.

"Convulsive" Properties. Cope and Hancock (1939) and Knoefel (1945) have noted that the conversion of a barbiturate to a thiobarbiturate frequently introduces stimulant properties, a hypnotic drug being converted into a convulsant. Richards (1951), studying this effect with several methyl-allyl and other substituted thiobarbiturates, observed a marked species difference in response to these drugs. Mixed sedative and convulsant activity was frequently observed in mice, the convulsant properties were predominant in rabbits, while sleep occurred when the drugs were given to monkeys. The series did not include thiopentone or other thiobarbiturates used in anaesthesia, but reports from other sources of animal experiments with these drugs reveal no convulsive properties (Adams, *1944*).

Wynne (1948) has described pronatory movements of the arm progressing to strong clonic contractions of the pectoral and neighbouring muscles following the injection of thiopentone in man. Occasionally these may spread to involve the muscles of the diaphragm and glottis. He drew attention to the similarity in structure between thiopentone and 5-ethyl 5-dimethyl barbituric acid, which is a convulsant. Scurr (1948) considered these movements to be a manifestation of the withdrawal reflex occurring when consciousness is lost, analagous to the behaviour in the second stage of anaesthesia with inhalation agents.

In 739 cases studied by Morton (1948) movements of the arm or shoulder followed the induction of anaesthesia with thiopentone in 40 patients. In 16 instances the movement was spontaneous, while in the others it was evoked by withdrawal of the needle,

application of an arm-splint or pulling forward the chin The incidence was related to the age of the patients, movements occurring in 38 8 per cent of cases with ages between 5 and 15 years as compared with one per cent. of the older patients Attention was also drawn to the possibility of premedication being an important factor Atropine and a barbiturate were given to children before operation while adults were premedicated with papaveretum and scopolamine.

The effect of premedication on the incidence of movement during the induction of anaesthesia with thiopentone has been studied by the author in 219 adult patients undergoing cystoscopy The thiopentone was given at a fixed rate in a 5 per cent solution the dose being approximately 40 mg /st. body weight. The needle was withdrawn in all cases immediately after the injection. The results are shown in Table XXIII When movement occurred, it was nearly always on withdrawal of the needle or swabbing the arm. There was a higher incidence of movement in patients who received atropine alone or combined with a barbiturate as pre medication. The difference between this series and those having an opiate or pethidine before operation was significant at a 5 per cent. level

(The findings suggest that the so-called convulsive properties of thiopentone are a manifestation of its lack of analgesic power) As mentioned above reflex movement can be abolished at a lighter level of narcosis with thiopentone when it is combined with analgesics such as nitrous oxide/oxygen or pethidine than when it is used alone. The same seems to be true during induction of anaesthesia. The response to withdrawal of the needle or any other stimulus may not be completely suppressed by the depth of anaesthesia induced with thiopentone but it is abolished when, in addition an analgesic drug is given as premedication.

Generalised muscular movements are more common during the administration of hexobarbitone than with the thiobarbiturates. They are not limited to movements of limbs but often take the form of a shudder of the whole body and may occur in deep anaesthesia in patients who are not subject to any exogenous stimulation. Although the incidence of movements with hexobarbitone is reduced by premedication with analgesic drugs and the use of nitrous oxide/oxygen, it is not completely eliminated

TABLE XXIII

Incidence of movement of the upper limb following induction of anaesthesia with thiopentone

Premedication Atropine plus	No of Cases	Sex		Average Age (years)	No of Patients showing Movement			Percentage
		Male	Female		Involving Shoulder Girdle	Pronation of Arm only	Total	
—	41	29	12	45	3	10	13	31·7
Opiate	105	76	29	46	1	0	1	1·0
Barbiturate	50	34	16	54	8	14	22	44·0
Pethidine	23	16	7	54	1	0	1	4·3
Analgesic	128	92	36	48	2	0	2	1·6
No analgesic	91	63	28	48	11	24	35	38·4

This is one of the reasons why hexobarbitone has been almost entirely replaced by thiopentone in clinical anaesthesia.

Local Analgesic Action. Schiller (1953) has shown that 4 per cent. amylobarbitone blocks conduction in peripheral nerves and relieves pain in deep tissue foci. The injections are no more painful than when procaine is used and subsequent local irritation is almost absent. The use of the drug is limited by the fact that only relatively small amounts can be given if hypnotic effects are to be avoided. Quinalbarbitone is an even more powerful local anaesthetic, but it is likely to cause tissue necrosis. Thiobarbiturates may have a local anaesthetic action *in vitro*, but are too irritant to be of any practical use.

Subarachnoid injections of barbiturate solutions cause spinal analgesia. Schiller found weakness in monkeys within 5 minutes of the injection of 5 per cent. amylobarbitone with complete paralysis in a further 5 minutes. The effects began to wear off half an hour after injection. Morrison, Koppanyi and Tuohy (1951) have used a 5 per cent. solution of thiopentone, rendered hyperbaric by the addition of 10 per cent. dextrose, for spinal analgesia in 10 patients. Sensory loss was observed within 3 to 7 minutes and motor anaesthesia, which was variable, from 5 to 12 minutes after injection. The initial dose varied from 3 to 4 ml., and to maintain anaesthesia 1 ml. was added every 20 to 30 minutes. A central soporofic effect was observed in all cases, varying from slight drowsiness to deep narcosis. Certain complications occurred after the spinal effects wore off one patient having retention of urine, and another having sensory loss over one leg for 4 weeks, with eventual recovery. Considering the safety of orthodox spinal analgesic solutions, it is unlikely that these observations will ever be of more than academic interest.

CARDIOVASCULAR SYSTEM

(**Heart Lung Preparation.** The depressant effects of thiobarbiturates on the myocardium are seen when the drugs are injected into the isolated heart lung preparation Prime and Gray (1952) describe the effect of 50 mg thiopentone as follows

Male dog weighing 9 kg Initial data heart rate 140 per min., aortic pressure (B.P) 85 mm. of mercury right auricular pressure (R.A.P) 0 cm. of saline, left ventricular output (C.O) 250 ml. per min.

After an injection of 5 ml. saline there was no alteration in the above data. Fifty mg of thiopentone dissolved in 5 ml. of saline were then injected. The response was dramatic. The R.A.P rose in the course of 15 seconds to 17 cm. of saline, whilst the B.P fell to 50 mm. of mercury The C.O fell rapidly and progressively to zero. The heart was greatly dilated and, in order to prevent complete collapse of the preparation, the venous inflow was clamped off A fairly rapid fall of R.A.P to about 9 cm. of saline resulted, and there was a gradual

TABLE XXIV

Effect of artificial respiration on the maximum tolerated dose of thiobarbiturates in the dog

(After Woods, Wyngaarden, Rennick and Seevers, 1949)

A—SMALL DOSES ADMINISTERED AT REGULAR INTERVALS

Drug	*Type of Respiration*	*Survival Time*	*Tolerated Dose of Thiobarbiturate*		*Elevation of Dosage (mg./kg./hr.) by Artificial Respiration*
		(mins.)	mg./kg	mg./kg./hr	%
Thiopentone	Spontaneous	240	91·3	22·8	—
Thiopentone	Artificial	285	159·9	33·2	45·6
Thiamylal	Spontaneous	230	64·6	16·8	—
Thiamylal	Artificial	180	96·3	24·5	45·6

B—CONSTANT RATE INTRAVENOUS INFUSION

Drug	*Type of Respiration*	*Survival Time*	*Total Dose*	*Elevation of Dosage (mg./kg.) by Artificial Respiration*
		(mins.)	mg./kg.	%
Thiopentone	Spontaneous	72	63·9	—
Thiopentone	Artificial	255	170·5	165
Thiamylal	Spontaneous	97·5	48·8	—
Thiamylal	Artificial	252	124·6	155

thiopentone anaesthesia. On the other hand Harrison (1949) detected irregularities of the pulse in one fifth of 500 patients anaesthetised with thiopentone and d tubocurarine chloride In a later communication (1953) she found a 21 per cent. incidence of arrhythmia during the first twenty minutes of anaesthesia with thialbarbitone as compared with 5 3 per cent. after thiopentone. Electrocardiographic studies in 52 patients showed the majority of arrhythmias to be ventricular extrasystoles.

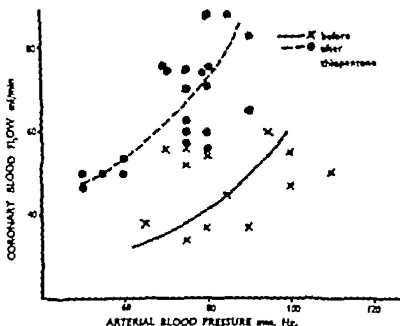


FIG. 20.—Coronary blood flow before and after thiopentone in the dog

Johnstone (1951) also found that the pulse irregularities during thiopentone anaesthesia are due to ventricular ectopic beats. He suggested that these arise in the presence of hypercarbia and disappear as soon as the carbon dioxide is eliminated. Hypercarbia develops rapidly during the respiratory depression which often accompanies induction with thiopentone. Although he did not compare the incidence of arrhythmias after thialbarbitone and thiopentone, Johnstone found that irregularities after the former drug may also be associated with carbon dioxide retention. He supports his hypothesis from studies with cyclopropane, trichlorethylene and di-vinyl ether (1952) With all these drugs hypercarbia is responsible for the appearance of ventricular arrhythmias

during anaesthesia. There is some evidence to show that changes in the plasma potassium as the results of hypercarbia may play a part in the aetiology of these irregularities (see p 184)

Heart Rate Many factors determine the pulse rate changes after thiobarbiturates. (Johnstone (1951) suggests that their general effect is to increase relatively slow rates and to decrease rapid rates.) In 50 patients who were premedicated with $\frac{1}{50}$ gr (1·3 mg) atropine, thiopentone induction reduced the heart rate from an average of 133 beats per minute to 122 per minute. In a similar group of non atropinised cases there was an average increase of 10 beats per minute after the barbiturate. Respiratory depression with the resulting hypoxia and hypercarbia will tend to increase the pulse rate.

(**Blood Pressure.** Peripheral vasodilatation occurs immediately after the injection of thiopentone (Fig 21) With an undamaged

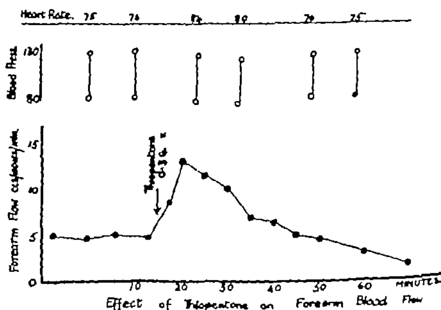


FIG. 21 —Effect of thiopentone on forearm blood flow (Prime and Gray 1952)

myocardium the blood pressure will be maintained by a compensatory quickening of the heart rate, although the pulse pressure may be increased. The exact mechanism of this vasodilatation is not known, but it is probably due to paralysis of the sympathetic nervous system by the effects of the drug on the vaso-motor

centre. Carbon dioxide retention which causes dilatation of the arterioles and capillaries is a contributory factor)

(The effect of thiobarbiturates on the blood pressure in man depends on the dose and rate of administration the state of the myocardium and the state of the peripheral circulation Both rapid injection and the use of large induction doses cause a profound fall in arterial pressure (Table XXV) This is partly due to peripheral vasodilatation but the toxic effects of the large dose of drugs on the myocardium impair its compensatory ability and may reduce the cardiac output) Clinical observations show that, as in the heart lung preparation patients with a damaged myocardium before injection will have more profound falls in blood pressure with smaller doses of thiobarbiturates than fit persons. Any pre-existing coronary insufficiency will be increased by the hypotension, cardiac hypoxia will further decrease the efficiency of the heart muscle, and a vicious circle is set up

Subjects with hypertension are also more susceptible to the depressant effects of thiobarbiturates, and this has been used as a prognostic test of the value of thoracolumbar sympathectomy Peripheral vasoconstriction, such as follows severe haemorrhage, will also be reduced by thiobarbiturates and the inadequacy of the circulating blood volume thus revealed will result in a sharp fall in the arterial blood pressure (see p 148) Where peripheral vascular tone is already partly abolished by ganglion blocking or

TABLE XXV

Effects of rapid injection of a barbiturate and relaxant on pulse rate and B.P Changes bear no relation to the nature of the relaxant

(Stephen, Martin and Nowill, 1953)

	Thiopentone	*Thiamylal*	*Hexobarbitone*
Patients	100	100	37
Dose (mg.)	200–1000	200–700	500–1000
Average	466	416	767
Increase in pulse (average)	16 (47 pts.)	17·2 (46 pts.)	25·7 (30 pts.)
Decrease in pulse (average)	13 (42 pts.)	15·0 (39 pts.)	21·0 (4 pts.)
No change	11 patients	15 patients	3 patients
Increase in B.P (average)	18–20 (2 pts.)	18 8–15·5 (9 pts.)	0
Decrease in B.P (average)	38·8–15·7 (88 pts.)	31 5 15·3 (72 pts.)	37·9–23·0 (37 pts.)
No change in B.P	10 patients	18 patients	1 patient
B.P fall 40 mm. systolic or more	33%	27%	39%

other vasodilator drugs, the hypotensive effects of thiobarbiturates are more marked. The use of the upright posture increases the severity and duration of the blood pressure falls. This applies particularly to elderly patients and those with disturbances of peripheral vascular tone. Severe hypotension is also more likely to occur in vagotonic patients or those who normally have a labile blood pressure.

Circulatory Dynamics. Price, Connor Elder and Dripps (1952) found tachycardia decreased mean atrial pressure and pulse pressure and diminished intrathoracic venous pressure after the administration of thiopentone. Inflation of the lungs with oxygen under 15 to 20 cm. of water pressure produces significantly greater arterial hypotension in subjects anaesthetised with thiopentone than in the same subjects during consciousness. This result is attributed to a relative failure of the vasomotor response to hypotension caused by thiopentone.

The effect of the combination of thiopentone/*d* tubocurarine/nitrous oxide/oxygen on circulatory dynamics has been studied in fit male subjects by Prime and Gray (1952) Premedication and apprehension of the operation caused a rise in the cardiac output. After the induction of anaesthesia it showed a tendency *to fall toward the initial level and remained* constant during the remainder of the operation. By contrast, forearm blood flow showed a sharp increase following upon the injection of thiopentone. The increase in each case was greatest during the ensuing ten minutes or so Blood pressures showed an initial slight fall with a widening of the pulse pressure in most cases, though these changes were not great. Heart rate was increased in all cases.

A comparison of the average effects of thiopentone/*d*-tubocurarine/nitrous oxide/oxygen with thiopentone/ether (with or *without nitrous oxide) and thiopentone/cyclopropane/oxygen* are shown in Table XXVI With ether there was an acceleration of both central and peripheral blood flow after induction, which fell off during the subsequent hour until values lower than the initial ones were reached. The effects of cyclopropane are similar to those of ether but the increases were maintained during the period of observation.

The above studies show that in spite of its cardiac toxicity the proper administration of thiopentone in normal man results in

TABLE XXVI

Average effects of three anaesthetic combinations on circulatory dynamics

(after Prime and Gray 1952)

	Cardiac Output	Forearm Blood Flow	Blood Pressure	Heart Rate	Right Auricular Pressure
	L/min.	ml./100 ml./min			cm. water
Thiopentone/d-tubocurarine/nitrous oxide-oxygen (15*)					
At rest	4·8	—	132/87	67	—
After premedication	6·7	5·5	132/87	71	—
After induction	5·0	17·5	129/75	82	—
Average of 3 readings, at 15 minute intervals during the first hour	4·6	6·1	128/74	81	—
Thiopentone/ether or thiopentone/nitrous oxide-oxygen/ether (10)					
After premedication	6·1	6·9	120/80	71	−1·5
15 minutes after induction	8·4	30·1	126/78	83	−1·0
30 minutes after induction	7·2	22·5	126/81	79	−1·3
45 minutes after induction	6·4	13·6	—	—	—
60 minutes after induction	5·1	6·4	115/79	78	−1·3
Thiopentone/cyclopropane/oxygen (6*)					
After premedication	4·8	4·2	116/81	93	−1·5
10 minutes after induction	8·1	17·2	120/77	91	−0·2
30 minutes after induction	8·7	19·3	120/77	91	−0·3
45 minutes after induction	7·8	16·2	—	—	—
60 minutes after induction	6·9	14·2	116/75	89	−1·3

* No of observations from which average is calculated.

F

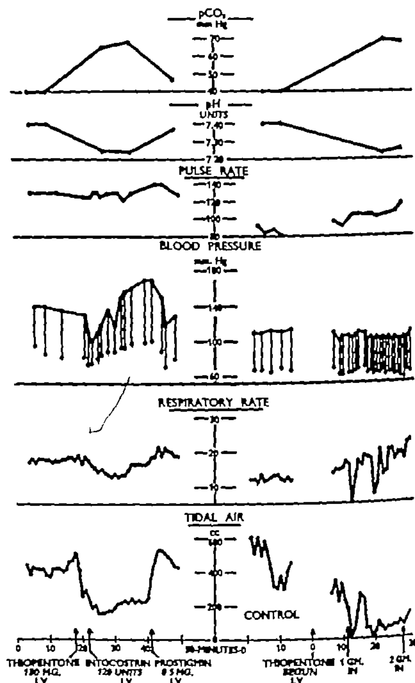


Fig. 22.—Effect of thiopentone and curare and thiopentone (pentothal) alone on arterial blood pH and CO_2 content, blood pressure, respiratory rate and tidal air

(Dripps, 1947)

the glottis is a reflex phenomenon, usually evoked by stimulation of the sensory side of the vagus by small amounts of mucus, regurgitated gastric contents or by foreign bodies such as an airway or a laryngoscope blade. It may also be initiated by stimuli from

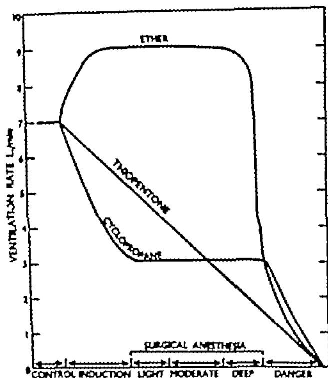


FIG. 23.—Variation in ventilation rate during anaesthesia with three different agents. The data for this figure were contributed by Drs. Patrick, Hunter Possati and Faulconer
(Ridley and Pender 1954)

other parts of the body such as stretching the anal sphincter, over-distension of the bladder or peritoneal traction. During deep anaesthesia these reflex arcs will be depressed centrally and spasm is probably no more common during deep thiobarbiturate anaesthesia than with other anaesthetic agents. The arc also can be broken on the sensory side by the use of topical analgesia, or on the motor side by the action of a muscle relaxant. (Laryngeal spasm is more likely to occur in vagotonic subjects and in children after induction with thiobarbiturates.)

These remarks similarly apply to the occurrence of bronchospasm after thiobarbiturates. If a predisposing cause, such as a foreign body or excess mucus in the trachea, is present before the

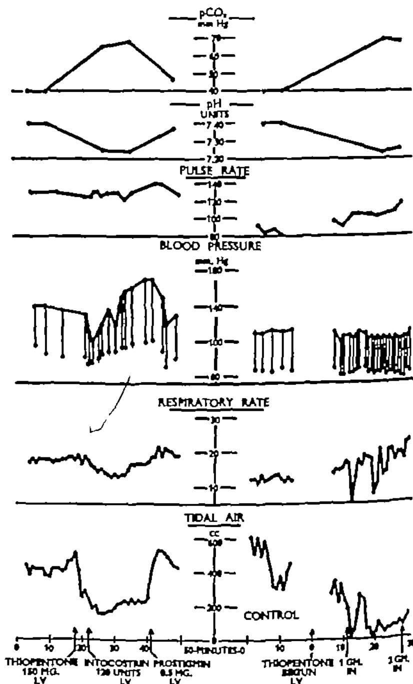


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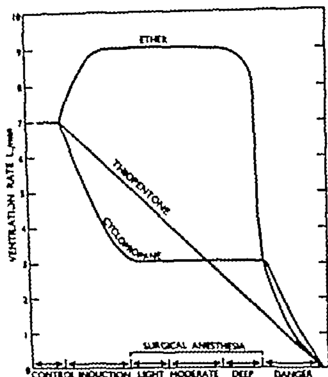


FIG. 23.—Variation in ventilation rate during anaesthesia with three different agents. The data for this figure were contributed by Drs. Patrick, Hunter Possati and Faulconer (Ridley and Pender 1954)

other parts of the body such as stretching the anal sphincter, over-distension of the bladder or peritoneal traction During deep anaesthesia these reflex arcs will be depressed centrally and spasm is probably no more common during deep thiobarbiturate anaesthesia than with other anaesthetic agents The arc also can be broken on the sensory side by the use of topical analgesia, or on the motor side by the action of a muscle relaxant. (Laryngeal spasm is more likely to occur in vagotonic subjects and in children after induction with thiobarbiturates)

These remarks similarly apply to the occurrence of bronchospasm after thiobarbiturates. If a predisposing cause, such as a foreign body or excess mucus in the trachea, is present before the

induction or during anaesthesia, then the administration of thiobarbiturates may lead to minor degrees of bronchospasm, but the drugs themselves do not initiate this condition. Reflex muscular spasm, involving the diaphragm and intercostal muscles, frequently occurs after intubation under a thiobarbiturate and closely stimulates bronchospasm. This probably plays a part in the sequence of events which is seen after the use of thiopentone and suxamethonium, when the effects of the relaxant wear off and a sufficient depth of narcosis has not been obtained with a supplementary agent. Johnstone (1955) has demonstrated that suxamethonium prevents bronchospasm in response to the stimulus of an endotracheal tube under light thiopentone anaesthesia. This does not apply to *d* tubocurarine chloride or laudexium, and if difficulty in inflation can be relieved by either of these drugs without deepening the anaesthesia, reflex muscle spasm rather than true bronchospasm is more likely to have been the cause. Gallamine triethiodide is intermediate in action between the above two groups of relaxants, and while it has some ability to prevent reflex bronchospasm it is not nearly as effective in this respect as suxamethonium.

The incidence of respiratory disturbances of vagal origin can be reduced by the judicious use of drugs which depress the laryngeal reflexes. Pethidine is one of the most important of these drugs in clinical use. It must be rememberd that it also depresses respiration, and a combination of thiopentone and pethidine produces a more marked effect than can be accounted for in a simple summation of the effects of the two drugs. This is perhaps explained by the analgesic action of pethidine in reducing the stimuli to respiration from the skin and tissues. The use of topical analgesia also reduces the incidence of laryngeal and bronchial spasm.

Clinical reports indicate that thiobarbiturates as a whole produce more respiratory disturbances than barbiturates. Stoelting, Graf and Rash (1950) observed less laryngospasm after quinalbarbitone than after thiopentone, and Volpitto (1951) found that side effects following intubation occurred less frequently after hexobarbitone than after thiopentone, thiamylal or Spirothal. The relative position of other anaesthetic agents is shown by the results of Adriani and Rovenstine (1943) who studied their effects upon bronchi and bronchioles of excised lung tissues (Table XXVII).

TABLE XXVII

In vitro responses of bronchi and bronchioles of excised lung tissue to various anaesthetic agents

(Adriani and Rovenstine 1943)

Drug	Number of different Animals from which Specimens were obtained: Rat	Dog	Man	Responses: Response to Drug alone	Atropine before Drug 1:250,000	Atropine following Drug 1:250,000	Eserine added after Drug 1:100,000	Procaine before Drug 1:50,000	Procaine followed by Drug 1:50,000	Total Observations	Remarks
Nitrous oxide (saturated)	3	1	0	+	U	R	+	U	R	18	Adrenaline and Ephedrine after drug produced relaxation.
Cyclopropane	4	2	1	+ + + +	U	R	+ + + + +	U	R	33	Do.
Thiopentone 1:10,000	3	1	1	+ + + + +	+	R	+ + + + + +	U	R	33	Do.
Hexobarbitone 1:10,000	2	1	1	+ + +	U	R	+ + + +	U	R	13	—
Pentobarbitone 1:10,000	2	1	1	+	U	R	+ +	U	R	13	—
Morphine sulphate	1	1	0	+	U	R	+ +	U	R	11	—
Diethyl ether	3	1	1	+ +	—	—	U	U	U	30	Larger concentrations constrict
C	2	1	0	+ +	—	—	U	U	U	20	Do.

\+ indicates constriction averaging approximately 4 per cent. of the diameter of the lumen.
U no modification by drug
R drug produces a relaxation of the contracted bronchial muscle

Diethyl ether and chloroform and probably nitrous oxide have no effect, morphia and pentobarbitone cause a very slight constriction while hexobarbitone, cyclopropane and thiopentone have a marked effect in the above increasing order of potency This is in full clinical agreement with the ability of these drugs to heighten laryngeal reflexes during anaesthesia.

REPRODUCTIVE SYSTEM

Clinical reports indicate that thiobarbiturates in therapeutic dosage neither depress nor increase the tone of the gravid uterus. Uterine muscle tone is depressed to a variable degree in deep anaesthesia with all agents, and there is some inhibition of contractions in light anaesthesia with chloroform and ether Muscle relaxants, which are frequently combined with thiobarbiturates in anaesthesia for Caesarian section, have little effect on the uterine musculature.

The effects of various anaesthetic agents upon Fallopian tube motility have been studied by Walker and Stout (1952) in a series of 359 Nigerian women. Thiopentone produced no effect on motility When combined with curare there was an increase in the amplitude of contractions. The relative position of other anaesthetic agents is shown in Table XXVIII. In this the mean increase or decrease of a tracing taken under anaesthesia is compared with the mean of two readings in the unanaesthetised state after premedication. The effects of morphine and atropine are compared with unpremedicated controls.

The above workers found that thiopentone had no effect on utero-tubal spasm. A spasmolytic effect was present with ether chloroform, trichlorethylene and probably nitrous oxide. Morphine, on the other hand caused increased spasticity

Thiobarbiturates affect the placental circulation only as a result of their action on the systemic blood pressure of the mother Periods of uterine contraction, if combined with maternal hypotension may result in foetal hypoxia.

Evidence from many sources indicates that barbiturates of varying structure pass through the cat and guinea-pig placenta in less than 5 minutes. Hellman *et al* (1944) studied the transmission of thiopentone in 7 cases Up to seven minutes after a single injection of the drug minimal amounts were found in the blood

TABLE XXVIII

The effect of various anaesthetics upon tubal motility

(Walker and Stout, 1952)

Cases	Series	Pressure	Contractility	Amplitude	Frequency
20	Ether	Decrease ++	Decrease +	N.S.	Increase +++
20	Chloroform	Decrease +	? Increase	? Increase	N.S.
20	Trilene	Decrease ++	N.S.	N.S	N.S.
20	Cyclopropane	N.S.	N.S.	N.S.	N.S
20	Nitrous oxide	N.S	? Increase	Increase +	? Increase
40	Thiopentone	N.S.	N.S.	N.S	N.S.
20	Curare	N.S.	N.S.	Increase +	N.S.
	Curare and thiopentone	N.S.	N.S.	Increase +	N.S.
20	High spinal	N.S.	? Increase	Increase +	N.S.
20	Low spinal	N.S.	N.S.	? Increase	N.S.
20	Morphia	N.S.	Increase ++	? Increase	N.S.
20	Atropine	N.S	? Increase	? Increase	N.S.

Classification N.S. Not 20 per cent. significance level.

? Not 10 per cent. significance level.

\+ Significant $0{\cdot}1 > p < 0{\cdot}01$ per cent

++ Moderately significant $0{\cdot}01 > p < 0{\cdot}001$ per cent.

+++ Highly significant $0{\cdot}001 > p < 0{\cdot}0001$ per cent.

For patency the significance is the same as for pressure the result being in the opposite sense

of the newborn infant. Equilibrium between maternal and foetal blood was reached within 10 to 12 minutes after induction of anaesthesia after this period the foetal level of thiopentone was very low

Cohen, Paulson, Wall and Elert (1953) estimated blood thiopentone levels in the mother immediately after the induction of anaesthesia (doses of 120 to 180 mg) for Caesarian section and the maternal and placental concentrations at the time of delivery of the baby The initial maternal level averaged 9·7 μg /ml. and at delivery was 4 7 μg /ml. with a placental concentration of 2·7 μg /ml. This indicated a 58 per cent. transmission of thiopentone across the placenta, with the foetal concentration only reaching 28 per cent. of the initial peak level attained in the mother Unfortunately these workers do not give the times of delivery of the baby in relation to the injection of thiopentone.

A similar investigation has been carried out by Kahn, Nicholson and Assali (1953) using thiamylal. Their results (Fig 24) indicate

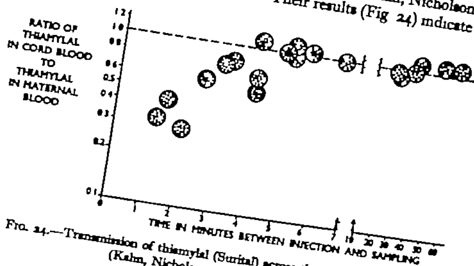


FIG. 24.—Transmission of thiamylal (Surital) across the placental barrier (Kahn, Nicholson and Assali, 1953)

that equilibrium between maternal and foetal blood was reached within 4 to 5 minutes after injection of the barbiturate, and that this equilibrium was maintained over a period of at least one hour

It is difficult to reconcile the results with thiamylal (Kahn *et al.*) and thiopentone (Hellman *et al.*) as regards time of maximum transmission of the drug It is unlikely that the difference in structure between the two compounds could account for the more

rapid transmission of thiamylal The technique used for estimation of thiamylal is not as specific as that employed in the thiopentone studies, but, as the authors point out, the error is only in the region of 1 per cent. with samples taken 5 minutes after induction of anaesthesia. One can be certain, however that there is a delay of at least 5 minutes in maximum transmission of barbiturates across the placental barrier By the time equilibrium has been reached between the maternal and foetal blood levels the peak concentration of barbiturates in the mother will have passed (Cyclopropane and ether traverse the placenta almost quantitatively, whilst only 60 per cent. of the nitrous oxide in maternal blood reaches the foetus. About 60 to 70 per cent. of pethidine crosses the placental barrier and it is generally agreed that *d*-tubocurarine chloride does not reach the foetal circulation.

As stated previously, the foetal respiration is particularly susceptible to the depressant effects of thiopentone.) Taylor, Govan and Scott (1951) found that when given 4 to 11 minutes before delivery, the drug depressed the ability of the infant to gain normal adult oxygen saturation. At the end of one hour the average saturation in 10 cases was 80 per cent., which was not significantly lower than that of infants born of mothers receiving no general anaesthetic agents, but in only two of the ten was the saturation value 90 per cent. or over at that time, while one required resuscitation.

(There is some evidence that sufficient amounts of barbiturates may be excreted in breast milk to cause drowsiness of the baby No information is available as regards the importance of this after the single dose administration of intravenous thiobarbiturates.)

LIVER FUNCTION

Using the bromosulphalein method, Habif Papper, Fitzpatrick, Lowrence, Smythe and Bradley (1951) observed a decrease in the estimated hepatic blood flow with an increase in the hepatic arteriovenous oxygen difference during anaesthesia with thiopentone or cyclopropane. Shackman, Graber and Melrose (1953) using a similar technique, showed that a 30 per cent. decrease in the estimated hepatic blood flow occurred with thiopentone/cyclopropane anaesthesia. This decrease was not related to changes in the arterial pressure, and represented an increase in splanchnic

vascular resistance. Contrary to the findings of Habif *et al*, they concluded that hepatic oxygen consumption was reduced by 34 per cent.

Reynolds *et al.* (1938) and Richards and Appel (1941) have shown that hepatic impairment follows the use of thiopentone in animals. The smaller the animal the more marked were the effects of the drug on the liver During prolonged thiopentone anaesthesia in dogs, Booker (1946) found a progressive decrease in the ability of the liver to remove bromosulphalein from the blood Walton, Uhl Egner and Livingstone (1950) found that small doses of thiopentone were mildly toxic to both the normal and damaged liver of the dog but this effect was due to hypoxia and could be overcome by adequate ventilation with oxygen. Doses of 20 mg /kg given twice daily to normal dogs for periods of 2 to 3 weeks caused a mild depression of hepatic function, as judged by the prothrombin time and serum bilirubin level, with complete return to normal four days after the last injection of thiopentone (Walton, Salamando and Egner, 1951) In contradistinction to the effects of small doses, adequate oxygenation did not reduce the toxicity of repeated large doses of thiopentone.

Using a battery of liver function tests, Pohle (1948) found that liver impairment occurred in 50 per cent. of cases after operation. Its occurrence was unrelated to the anaesthetic agent used, and the effects of thiopentone did not differ from those of chloroform. Unfortunately the doses of thiobarbiturate used were not recorded. The patients he studied were in poor general condition before operation and he suggested that their nutritional state and the occurrence of hypoxia after the operation were the important factors in the aetiology of liver damage. Fairlie *et al.* (1951) examined the effects of anaesthetics (excluding thiobarbiturates) and also found no significant difference in the effects of various agents on the liver

A much quoted case, reported by Vaizey (1938), describes the occurrence of jaundice following thiopentone, but the evidence incriminating the drug is not very convincing The hippuric acid excretion test, urobilinogen metabolism and blood-sugar levels were examined by Mordvinova (1948) before and after thiopentone anaesthesia in 80 cases. The detoxicating function was significantly lowered in 17 patients, pigment metabolism was upset in 31 cases and blood-sugar levels were abnormal in 17 subjects.

Recovery to normal took as long as two weeks in some instances.

In contrast to the above findings, Carraway (1939), using the hippuric acid excretion test, found no alteration in liver function after thiopentone in 100 cases. Many of these patients were jaundiced or had liver damage before operation Using the same test, Boyce and McFetridge (1938) found that ether ethylene and spinal analgesia all had a marked effect on liver function for the first seven days after operation

(The lack of agreement by various workers as to the hepatotoxic properties of thiopentone is probably due to the fact that many factors other than the anaesthetic agent, may adversely affect the liver function before, during and after anaesthesia. Upper abdominal section has more deleterious effects than lower abdominal or non abdominal operations The longer the duration of the procedure, the more likely is liver damage to occur Chronic sepsis, pulmonary tuberculosis, thyrotoxicosis, intestinal obstruction, advanced carcinoma and severe burns all cause impairment of hepatic function. Hypoxia and hypotension during anaesthesia are also contributory factors and the occurrence of complications during convalescence likewise increases the risk of liver damage.)

The author (1955) has avoided these variables by comparing urinary urobilinogen excretion for the first three days after operation in two series of patients, in one series thiopentone was used as the main anaesthetic agent (average dose 1 17 g), and in the other it was reserved for the induction of anaesthesia (average dose 440 mg) The series were strictly comparable as regards the nature and duration of operations, the age and sex of the patients, premedication and post-operative sedation. No case was included in whom there was present any factor that might adversely affect liver functions before, during or after anaesthesia. The findings (Table XXIX) revealed a significantly higher urinary excretion of urobilinogen in patients who received large doses of thiopentone. By excluding intravascular haemolysis, as a possible factor in this increased urobilinogin output, the author concluded that liver dysfunction occurs in an appreciable number of patients when doses of thiopentone exceeding 750 mg are administered The incidence of hepatic damage is related to the dose of thiobarbiturates given (Fig 25). The use of muscle relaxants does not increase the hepatic toxicity of thiopentone, provided respiratory depression and hypoxia do not occur

TABLE XXIV

Post-operative excretion of urobilinogen in 464 cases half of whom received thiopentone as the main anaesthetic agent in the remaining half it was used only as an induction agent

(Dundee, 1955)

Operation	No. of Cases in each Series	Post-operative Urobilinogen Excretion						Difference between Series			
		Thiopentone as Main Agent (Number of Cases)			Thiopentone for Induction only (Number of Cases)			+		±	
		+	±	−	+	±	−	χ^2	p	χ^2	p
Dilatation and curettage	84	20	44	40	5	6	78	259·2	<·001	47·9	<·001
Inguinal hernia repair	44	28	36	8	7	9	35	101·8	<·001	74·9	<·001
Varicose vein ligation	18	5	14	4	0	1	17	178·9	<·001	26·4	<·001
Appendicectomy	15	7	12	3	4	4	11	21·8	<·001	3·1	<·05 >·01
Lumbar sympathectomy	13	8	10	3	3	3	10	23·3	<·001	10·4	<·01
Plastic operations	11	7	10	1	1	1	10	89·1	<·001	39·6	<·001
Haemorrhoidectomy	11	8	11	0	3	4	7	17·3	<·001	11·5	<·001
Hydrocele	10	8	8	2	0	0	10	70·4	<·001	70·4	<·001
Hysterectomy	9	6	7	2	0	0	9	54·4	<·001	40·0	<·001
Thyroidectomy	8	4	8	0	2	2	6	24·0	<·001	2·7	<·2 >·1
Incisional hernia repair	6	3	4	2	0	0	6	18·7	<·001	10·7	<·01
Meniscectomy	3	1	2	1	0	0	3	5·3	<·05	1·3	<·3 >·2
Totals	232	105	166	66	25	30	202	708·1	<·001	286·9	<·001

\+ signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 20 on the second and third post-operative days.

± signifies that urinary urobilinogen was detected in a dilution of greater than 1 in 15 on either the second or the third-post-operative day

p probability of difference in urinary urobilinogen excretion between the two series having occurred by chance.

Nitrous oxide, ethylene and cyclopropane produce no impairment of liver function if hypoxia is avoided their toxicity is comparable with that of small doses of thiopentone. Divinyl ether produces a very slight effect, but diethyl ether causes a distinct

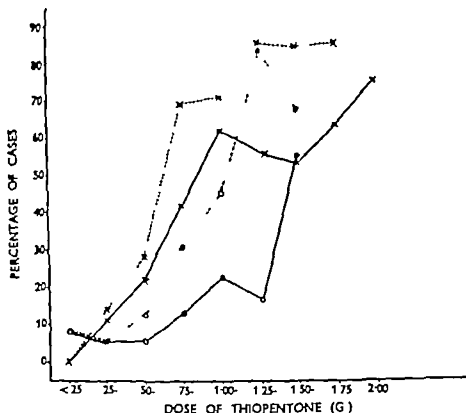


FIG. 25.—Correlation between the incidence of hepatic dysfunction and dose of thiopentone administered.
O patients undergoing dilatation and uterine curettage.
X abdominal operations.
-- possible liver impairment (urobilinogen excretion ±)
— definite liver impairment (urobilinogen excretion +)
(Dundee, 1955)

impairment of function lasting for more than 24 hours. A prolonged period of liver damage follows the use of chloroform, although recent reports suggest that much of this is due to hypoxia. The effect of thiobarbiturates, other than thiopentone, on liver function in man has not been studied. Since all these compounds are inactivated in the liver as is the case of thiopentone, hepatic dysfunction is likely to follow the use of large doses.

TABLE XXIX

Post-operative excretion of urobilinogen in 464 cases half of whom received thiopentone as the main anaesthetic agent in the remaining half it was used only as an induction agent

(Dundee, 1955)

Operation	No. of Cases in each Series	Post-operative Urobilinogen Excretion: Thiopentone as Main Agent (Number of Cases)			Thiopentone for Induction only (Number of Cases)			Difference between Series: +		±	
		+	±	−	+	±	−	χ^2	p	χ^2	p
Dilatation and curettage	84	20	44	40	5	6	78	259·2	<·001	47·9	<·001
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Lumbar sympathectomy	13	8	10	3	3	3	10	23·3	<·001	10·4	<·01
Plastic operations	11	7	10	1	1	1	10	89·1	<·001	39·6	<·001
Haemorrhoidectomy	11	8	11	0	3	4	7	17·3	<·001	11·5	<·001
Hydrocele	10	8	8	2	0	0	10	70·4	<·001	70·4	<·001
Hysterectomy	9	6	7	2	0	0	9	54·4	<·001	40·0	<·001
Thyroidectomy	8	4	8	0	2	2	6	24·0	<·001	2·7	<·2 >·1
Incisional hernia repair	6	3	4	2	0	0	6	18·7	<·001	10·7	<·01
Meniscectomy	3	1	2	1	0	0	3	5·3	<·05	1·3	<·3 >·2
Totals	232	105	166	66	25	30	202	708·1	<·001	286·9	<·001

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p probability of difference in urinary urobilinogen excretion between the two series having occurred by chance.

Nitrous oxide ethylene and cyclopropane produce no impairment of liver function if hypoxia is avoided their toxicity is comparable with that of small doses of thiopentone. Divinyl ether produces a very slight effect, but diethyl ether causes a distinct

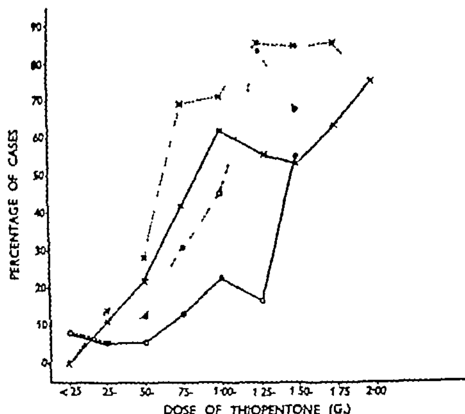


FIG. 25 —Correlation between the incidence of hepatic dysfunction and dose of thiopentone administered.
O patients undergoing dilatation and uterine curettage.
X abdominal operations.
-- possible liver impairment (urobilinogen excretion ±).
— definite liver impairment (urobilinogen excretion +)
(Dundee, 1955)

impairment of function lasting for more than 24 hours. A prolonged period of liver damage follows the use of chloroform, although recent reports suggest that much of this is due to hypoxia. The effect of thiobarbiturates, other than thiopentone, on liver function in man has not been studied. Since all these compounds are inactivated in the liver as is the case of thiopentone, hepatic dysfunction is likely to follow the use of large doses

The action of thiobarbiturates on blood sugar is discussed in the section dealing with metabolism.

RENAL FUNCTION

The effects of thiobarbiturates on the kidney have not been as fully investigated as their action on liver function. Maloney *et al.* (1950) found that glomerular filtration was high in dogs during light thiopentone anaesthesia, but became depressed during deep narcosis. Their findings concerning effective renal plasma flow were inconclusive. Adriani (1946) states that oliguria during the period of anaesthesia is followed by polyuria, urinary output returning to normal within 6 to 8 hours.

In the studies of Habif *et al.* (1951), the glomerular filtration rate was measured by the inulin clearance and the effective renal plasma flow by the P.A.H. clearance. All values fell promptly during induction with thiopentone and there was little further alteration during the subsequent surgical operations. The electrolyte and water reabsorption increased. Recovery was almost complete when consciousness was regained. Their results demonstrated a vasoconstrictor response in both the kidney and liver with all forms of anaesthesia, associated with a fall in filtration, urinary concentration, excretion of electrolytes and urinary output.

De Wardener (1955) emphasises that, except when there is little or no renal blood flow, urinary output bears little relationship to the amount of blood flowing through the kidney. The rate of urine flow is dependent mainly on the concentration of circulating antidiuretic hormone, which in turn depends on the activity of the supraoptico-hypophyseal system. Nearly all anaesthetic agents stimulate this system, and the amount of urine passed during anaesthesia is therefore minimal (0·1 to 0·5 ml./min.), irrespective of any changes occurring in the renal circulation. Some of the action of thiobarbiturates may be secondary to the effect of these drugs on the cardiovascular system, the renal circulation being very sensitive to the blood pressure changes which are liable to occur with the thiobarbiturates.

Temporary oliguria may account for the slight rise in blood urea found by Ruth *et al.* (1939) in 25 unselected patients during and immediately after thiopentone anaesthesia. These changes

are so small that they were not detected by Adriani (1946) The author (1952b) did not observe any increase in blood urea during a two-hour period in patients anaesthetised with thiopentone/nitrous oxide/oxygen/*d* tubocurarine. Only when hyperventilation resulted in gaseous alkalosis, with constriction of renal vessels, were any changes found in the blood urea level, and even under these circumstances the rise was very small!

Silvette (1941) found that thiopentone inhibited the diuretic response to hypotonic sodium chloride and xanthine derivatives in rats. It had no effect on the efficacy of a mercury diuretic. The administration of thiopentone after posterior pituitary extract did not abolish the antidiuretic effect of the latter, but if the two drugs were given together no antidiuresis occurred.

(No histological evidence of kidney damage has been reported after the use of thiobarbiturates.

Ether and cyclopropane produce a marked reduction in renal blood flow This effect becomes more pronounced at deeper levels of narcosis. It is not influenced by prolonging the anaesthesia and it disappears rapidly at the end of administration.)

METABOLISM

Oxygen consumption falls during thiobarbiturate narcosis, the degree of depression being proportional to the depth of anaesthesia. *In vitro* studies by several workers have demonstrated a fall in oxygen consumption of brain liver and kidney slices by thiopentone, the degree of depression again being proportional to the concentration of the drug

A mild hyperglycaemia has been observed in animals during thiopentone anaesthesia by Hrubetz and Blackberg (1938) and Richards and Appel (1941) Booker and his co-workers (1946, 1949 1952) have verified this finding in dogs and studied the effects of thiopentone on carbohydrate metabolism. Liver glycogen in dogs on normal diets was found to be progressively depleted during long anaesthesia. The administration of glucose prior to the induction of anaesthesia produced hyperglycaemia and glycosuria. Even animals whose livers were depleted of carbohydrate by starvation before the induction of anaesthesia were unable to convert glucose to glycogen and remained hyperglycaemic. Intermediate metabolism of carbohydrates is also

depressed during prolonged thiopentone anaesthesia, as shown by a rise in the blood lactic acid content. All these changes could be mitigated by the use of small doses of insulin, if given along with or immediately *following the administration of thiopentone.*

These workers also detected disturbances in the intermediate metabolism of proteins. Amino-acids given intravenously led to an increase in the blood level, which remained high in anaesthetised animals, in *contradistinction to the controls in which it rises* during the first hour and returns to normal by the second hour

An interesting observation was that animals on a high carbohydrate diet and given insulin during anaesthesia required more *thiopentone* to maintain a constant level of narcosis than animals on a normal diet. Animals on high protein diet, on high carbohydrate diet and on normal diet with insulin given before and during anaesthesia follow in the above order as regards the thiopentone *requirements during anaesthesia (Table XXX).* The findings show the importance of adequate nutrition in the detoxication of the drug

TABLE XXX

Doses of thiopentone required to maintain a constant level of narcosis in dogs on various diets

(Booker Maloney Tureman and Ratcliff 1952)

Experimental Nutritional State	*No. of Experiments*	*Thiopentone Required (3 hours)*	*p*
		mg./kg.	
Normal diet	8	44·62	—
Normal diet+insulin	8	57·05	·02
High carbohydrate diet	6	57·66	·01
High carbohydrate diet+insulin	6	78·33	·03
High protein diet	6	62·88	·02

It is generally agreed that slight hyperglycaemia occurs during thiopentone narcosis in man. *This is of no clinical importance,* being similar to that observed with cyclopropane, and its effects are much less than those of ether or chloroform. Ether hyperglycaemia is inhibited by induction with thiopentone (Bass, Watts and Chase, 1953) The *author has found that patients*

under thiopentone/nitrous oxide/oxygen behave in a similar manner to those receiving thiopentone alone.

Stern *et al* (1945) have reported that glucose tolerance is decreased by thiopentone. They administered 1 5 g of 50 per cent. glucose intravenously to three subjects who had been anaesthetised for 45 to 60 minutes, and found a greater rise in blood sugar than when the same amount of glucose was administered in the conscious state. Their findings suggest a similarity in behaviour in humans and in dogs under thiopentone anaesthesia, with respect to glycogenesis. These observations are open to criticism in that the three patients were admitted to hospital with acute alcoholism and their livers may not have been in a normal condition.

The author has carried out a similar study in 6 healthy subjects. Blood sugar was estimated on three occasions in each person, (a) during thiopentone anaesthesia in the fasting state (b) after 50 g glucose without anaesthesia, and (c) during thiopentone anaesthesia induced after the oral administration of 50 g glucose. A typical finding is shown in Fig 26, the dose of thiopentone being 1·3 g administered over an hour and a half on both occasions. The results were all in agreement with those of Stern and his colleagues in man and Booker *et al.* in dogs. Booker *et al.* suggest this is a manifestation of the hepatotoxic action of thiopentone and cites it in support of the detoxication of the drug by the liver Beecher (1938) suggests that depression of centres near the thalamus or hypothalamus *may* be partly responsible for the blood-sugar changes which occur during barbiturate narcosis.

INTESTINAL TRACT

Gastric emptying time has been shown to be increased after various barbiturates in the dog Gruber and Gruber (1941) found that 20 mg /kg thiopentone and 40 mg /kg thioethamyl, when injected intravenously, may cause complete cessation of action of the pylorus and stomach. Temporary stimulation of tonus was followed by a depression of activity lasting during the period of deep anaesthesia. In some animals an increase in general tonus was again observed during the recovery period.

Golden and Mann (1943) have studied the effect of various

drugs on the tone and motility of the small intestine of the dog using loops of jejunum and ileum exteriorised in continuity and enclosed in bipedicled tubes of skin The slow injection of small

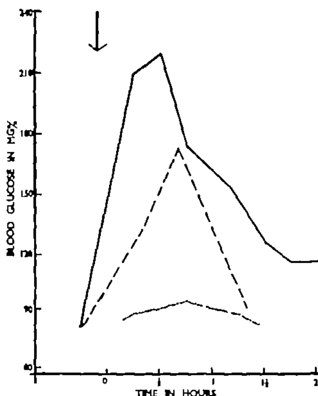


FIG. 26.—Effect of thiopentone on Glucose tolerance curve.
— — Thiopentone anaesthesia, 1·3 g given over 90 mins.
— — Glucose tolerance curve (no anaesthesia).
——— Glucose tolerance curve under thiopentone (same dose as above).
↓ 50 g. glucose given by mouth.
(All observations were made on one subject.)

doses of thiopentone had no effect on intestinal motility (Fig 27) With rapid injection there was a marked loss of tone and cessation of movement persisting for about half the duration of the sleep When food was given immediately after recovery from thiopentone, the normal pattern of peristalsis occurred, irrespective of the dose or rate of administration of thiopentone.

The slow injection of thiopentone followed by a 50 per cent. nitrous oxide/oxygen mixture had no effect on intestinal motility However when the administration of ether followed thiopentone,

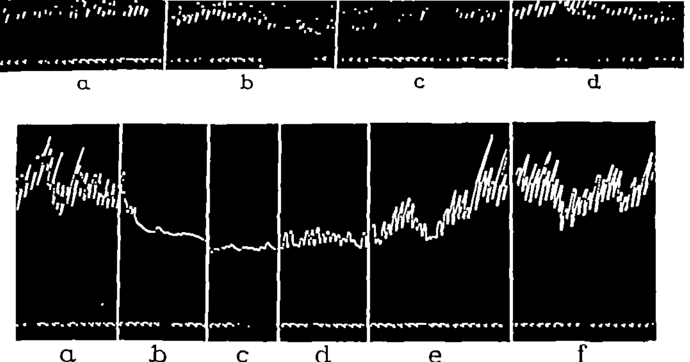


FIG. 27.—Effect of thiopentone on activity of a loop of ileum.

Slow Injection (upper tracing).

(a) Normal control.
(b) Immediately after completion of injection.
(c) 10 mins. after injection.
(d) 30 mins. after injection.

Time marked in 5-second intervals.

Rapid Injection (lower tracing).

(a) Normal control.
(b) During injection.
(c) 5 mins after injection.
(d) 8 mins. after injection.
(e) 10 mins. after injection.
(f) 20 mins. after injection.

(Golden and Mann, 1943)

bowel tone was decreased and motility ceased, similar to the effects observed with ether alone. The results of Golden and Mann with nitrous oxide show the deleterious effects of cyanosis and anoxia during anaesthesia. In clinical practice the pre-operative administration of opiates and atropine appears to be the most important factor influencing the activity of the small intestine.

MUSCLES AND MYONEURAL JUNCTION

Gross and Cullen (1943) observed that thiopentone decreased the contraction of the gastrocnemius muscle, elicited by the intra arterial injection of acetylcholine or electrical stimulation of the nerve, in the dog The depression of acetylcholine-induced contraction was not abolished by sectioning the nerve to the muscle. This suggests that thiopentone has some curariform action which was much less marked than with ether and which occurs only when very large doses are used. Comroe, Dripps, Bothello and Metz (1947) carried out electromyographic studies after stimulation of the ulnar nerve in humans. With blood concentrations of ether in the region of 100 to 120 mg per cent the action potentials of the muscles were reduced as with *d* tubocurarine, while clinical doses of thiopentone and cyclopropane had only a very small effect. Secher (1951) using the phrenic nerve-diaphragm preparation of the rat, found that barbiturates but not thiobarbiturates, produced a depression of myoneural transmission

Kraatz and Gluckman (1954) demonstrated an increase in muscle contraction after various barbiturates. The thiobarbiturates (thiopentone, thiamylal and thioethamyl) were most active in this respect, and the relative potency of a particular barbiturate was parallel to its general pharmacological potency and protein binding affinity They postulated that this was probably due to a direct action on the muscle fibre. A curare-like action was also demonstrated, and again this was more marked with thiobarbiturates.

The above work has been criticised by Sirnes (1954) on the grounds that physiological muscle contractions in the living organism are never single contractions. He carried out investigations in intact and isolated muscles of rabbits and rats using a frequency

of stimulation varying between 1 and 300 per second The drugs studied included thiopentone and thialbarbitone. He confirmed that an increase in muscle contraction was produced by relatively low concentrations of barbiturates. This increase occurred irrespective of whether the muscle contraction was induced by direct or indirect stimulation It appeared to be due to the fact that barbiturates cause a prolongation of the contraction time of muscles. With larger doses of the drugs the direct stimulant action on muscles was masked by the simultaneous occurrence of depression of myoneural transmission This latter was detected with doses of thiopentone and thialbarbitone not exceeding those used for the production of surgical anaesthesia in the animals. A synergistic effect was noted between thiopentone and *d*-tubocurarine chloride. As a result of his studies, Sirnes has suggested that part of the respiratory depression which occurs in barbiturate overdose is due to the peripheral action of the drugs In regard to this work, it must be pointed out that the effects of direct and indirect stimulation of the muscles were compared alternatively on the same preparation. Because of the intact motor end-plate one cannot be certain that the results of direct stimulation did not also show some effects resulting from impulses arising at the myoneural junction.

(Clinically the curariform effect of doses of thiobarbiturates used in anaesthesia is not as obvious as that of ether It may however explain the ease with which endotracheal intubation may be carried out following the use of thiopentone alone in subjects suffering from myasthenia gravis. No marked potentiation of *d* tubocurarine chloride by thiopentone has been reported to date, and the two drugs have been combined in anaesthesia with perfect safety)

BLOOD

Because of the high alkalinity of solutions, thiobarbiturates cause *in vitro* haemolysis, visible to the naked eye, when added to blood to a final concentration of as low as 1 1000 Using the method for detecting intravascular haemolysis based on the presence of carbonic anhydrase in the urine (Robinson 1950), the author (1955) studied the effect of varying doses of thiopentone in 40 patients. When thiopentone was used as the main anaesthetic

agents, evidence of haemolysis was detected in 20 per cent. of cases, and in 15 per cent. when it was used only for induction of anaesthesia. On analysis of the results the incidence of haemolysis seemed to be related to the nature and duration of the operation rather than to the dose of thiopentone. In all of these cases the degree of haemolysis was so slight that the absorption spectrum for haemoglobin could not be detected. There are no reported cases of haematuria after thiobarbiturates, and there is no evidence to suggest that the degree of intravascular haemolysis referred to above is of any clinical significance.

It is generally believed that barbiturates tend to cause haemodilution. This is based mostly on observations in animals before and after amylobarbitone or pentobarbitone, but some studies have included thiopentone. Haemodilution has been attributed to dilatation of the spleen, which is maximal 20 minutes after induction of anaesthesia with thiopentone in dogs (Hausner Essex and Mann, 1938) In man, opinions are not unanimous, Pender and Lundy (1944) having found a reduction in haemoglobin after thiopentone, while the author (1952a) reported no appreciable changes in the haematocrit, haemoglobin, erthrocyte count and oxygen capacity during the first twenty minutes of anaesthesia in 48 patients.

It is improbable that the spleen influences the blood concentrations in man to the same extent as in the dog Harris (1951) who agrees with this view has not been able to find any alteration in the size of the spleen during anaesthesia. Table XXXI shows the results of a comprehensive study of the effects of various agents in man. These results were verified with similar findings in the haemoglobin levels and oxygen capacity A slight haemodilution followed all agents and combinations studied, the changes being most marked with thiopentone which, with thiopentone/nitrous oxide/oxygen/ether showed the greatest scatter in readings. Only in patients who were anaesthetised with balanced anaesthesia (thiobarbiturate/relaxant/nitrous/oxide/oxygen/pethidine or ether) was the degree of haemodilution statistically significant.

MISCELLANEOUS

Allergy A transient urticarial rash is sometimes seen following the use of thiobarbiturates. It involves the upper chest and

Table XXXI

The effect of various anaesthetics on the haematocrit readings in man

Anaesthetic Agents	Intravenous only			Inhalation only		Intravenous Inhalation			Balanced
	Thiopentone	Thialbarbitone	Hexobarbitone	N_2O-O_2	Ether or N_2O-O_2-Ether	Thiop-N_2O O_2-Ether	Thiop-N_2O_2-Trilene	Thiop-C_3H_6	
No. of Cases	55	14	32	30	32	40	30	23	73
Packed Cell Volume % Control	45·06	41·77	45·80	42·35	42·54	42·52	42·80	43·14	45·55
Minutes after induction 5, 10, 15, 20, 30	44·86 44·40 44·30 44·40	41·11 40·40 40·50 41·00	45·93 45·10 45·21 45·21	42·43	42·32 41·87 42·10 41·90	42·16 41·91 41·56 41·47	42·30 42·38 42·40 41·80	43·42 42·88 42·50 42·25	45·33 45·20 45·19 44·71
Average maximum change as percentage of control	−1·06 ±0·69	−0·31 ±0·43	+0·16 ±0·43		−0·36 ±0·32	−0·74 ±0·80	−0·45 ±0·40	−0·58 ±0·32	−0·50 ±0·22
Percentage cases showing no change (±2%)	84	82	72	83	63	73	74	66	74
haemodilution (> −2%)	13	9	19	7	25	22	20	30	21
haemoconcentration (> +2%)	3	9	9	10	12	5	6	4	5

sometimes extends to the neck and face. This is probably a true allergic response to the drugs.

Delayed reactions to thiopentone have been reported by Lemere, Bearard and O'Hollaren (1952) in 32 out of 1027 patients given an average of 15 administrations of thiopentone as an adju vant to the treatment of chronic alcoholism. The most common was general malaise with aching weakness and fever up to 104 F This reaction came on from 1 to 24 hours after thiopentone and lasted from 1 to 5 days unless treated. It sometimes appeared after the first treatment, but usually manifested itself with increasing severity after several treatments had been given. Generalised skin rashes, joint pains and in one case a monoarticular arthritis were also observed. The prompt response of these reactions to A.C.T.H. suggests that they may be allergic in origin, but infection from syringes or needles has not been excluded. They have not been observed when amylobarbitone has been substituted for thiopentone.

The fact that delayed reactions after thiopentone have only been reported once in the literature does not necessarily mean that their incidence is very low After operation other more likely causes are sought to explain the occurrence of pyrexia and other reactions. This also applies when the drug is used with electroconvulsive therapy

Local Irritation. Thiobarbiturates are highly irritant if injected into subcutaneous tissues or arteries Tissue necrosis or fibrosis may occur in the former and spasm often followed by thrombosis in the latter The more concentrated the solution the more likely are severe sequelae to occur After intravenous injection thrombosis occurs in a small percentage of cases, most often in elderly debilitated patients. Again the incidence is higher when more concentrated solutions are used.

Rectal Administration. The onset of sleep occurs within 10 to 15 minutes after the rectal administration of thiobarbiturates. Thiopentone has been widely used as a basal narcotic for children the sequel of cerebral depression being the same as after intra venous injection, save for the delay in onset of narcosis. Because of the slower rate of absorption into the blood stream, blood pressure changes are usually less than after intravenous injection. Although one might expect proctitis to follow the use of such irritant solutions, no case has been reported by Weinstein and

Light (1948) in a series of 2500 rectal administrations of thiopentone.

Synergism with Curare Clinical reports which appeared soon after the introduction of curare suggested that this substance has some central action and potentiates the narcotic effect of anaesthetic agents Paulson and Essex (1949) who investigated this synergism in animals, *found no difference in the sleeping* time with thiopentone alone with thiopentone-curare or with thiopentone-mephenesin mixtures Curare has been shown to have no effect on the plasma thiopentone levels at which various signs of anaesthesia appear, nor does it alter the usual plasma time curve for the drug (Mark Papper, Brodie and Rovenstine, 1949)

Experiments carried out in two human volunteers by Gray, Gregory Rees and Fenton (1951) show that the administration of 15 mg *d* tubocurarine chloride before, or immediately after, 500 mg. thiopentone slightly shortens or has no effect on the duration of action of the narcotic. A brief period of apnoea always followed the thiopentone, but when *d* tubocurarine was injected first, complete apnoea was absent on several occasions. They attributed this difference to the stimulant action of *d* tubocurarine on the vital medullary centres. An alternative explanation is that respiratory depression caused by the relaxant may lower the plasma *p*H and increase the rate of diffusion of thiopentone. In support of this view is the observation of Kiersey *et al* (1951) that *d* tubocurarine does not affect the electroencephalographic changes produced by thiopentone

The synergistic action of thiopentone and competition blocking muscle relaxants at the myoneural junction have already been discussed.

Vomiting It is generally agreed that thiobarbiturates cause less vomiting than the inhalation anaesthetics. Some of the evidence in support of this view is given in Table XXXII On closer examination of published figures of the incidence of vomiting it became apparent that in most cases no allowance had been made for the nature and duration of the operation, the age and sex of the patient, the premedication and post-operative sedation or the pre and post-operative regime as regards the oral administration of fluids. These omissions markedly decrease the value of the observations.

TABLE XXXV

A comparison of the duration of narcosis with equal doses of thiopentone and thiamylal in the rat. The same series of animals were used for each drug but because of the smaller percentage of those falling asleep with thiopentone the reading had to be repeated in some of these so that the number from which the average was obtained would be approximately the same for each drug

(Dundee, 1955b)

Dose of Thiobarbiturate in mg./kg	Thiopentone			Thiamylal			Duration with Thiopentone ÷ Duration with Thiamylal
	No of Animals	% Asleep	Average Duration of Narcosis (mins.)	No of Animals	% Asleep	Average Duration of Narcosis (mins.)	
24	96	44	3·8 ± 0·3	53	66	8·7 ± 1·06	0·44
32	127	54	16·0	121	85	29·4	0·54
40	111	69	27·5 ± 1·34	102	80	36·4 ± 1·85	0·74
48	24	100	64·0 ± 12·00	24	100	64·0 ± 15·00	1·00

SUMMARY

Thiobarbiturates rapidly reach the central nervous system after intravenous injection, and the sequence of depression is similar to that seen with other anaesthetics. Because of their lack of analgesic action the signs and stages of anaesthesia are not so reliable with thiobarbiturates as with ether. This difference is also partly due to the irritant effect of ether on the tracheobronchial tree providing a stimulus to which the patient responds in a constant manner for any given degree of cerebral depression. Acute tolerance occurs to the narcotic effects of thiobarbiturates and the plasma level of the drug at which consciousness returns increases with the duration of the anaesthesia. The higher the initial concentration of the drug to reach the brain the greater will be the plasma level at which the various signs of anaesthesia occurs.

Thiopentone decreases cerebral oxygen consumption the degree of depression being proportioned to the depth of narcosis. Because of carbon dioxide retention cerebrovascular resistance is decreased and cerebral blood flow is increased. It is thought that anaesthesia is due to interference with a step in the carbohydrate metabolism of cerebral cells. Sodium succinate is not an effective antidote to thiopentone anaesthesia. The movements which are sometimes seen during the induction of anaesthesia are a manifestation of the lack of analgesic properties of thiopentone.

Thiobarbiturates block conduction in motor and sensory nerves, but this action is only of academic interest.

Thiopentone is a direct myocardial depressant, the degree of depression being proportional to the amount of drug in contact with the heart. Repeated injections have a cumulative effect on the myocardium and the unhealthy heart is more susceptible to the drug.

Cardiac arrhythmias following the use of thiobarbiturates are mostly ventricular in origin and are associated with hypercarbia. Peripheral vasodilatation occurs immediately after the injection of thiopentone. In subjects with a healthy cardiovascular system the judicious use of thiobarbiturates have little effect on cardiovascular dynamics, but severe hypotension may follow their rapid injection.

Thiobarbiturates are more profound depressants of respiration than any other drugs used in anaesthesia. The sensitivity of the respiratory centre to carbon dioxide is depressed in proportion to the depth of anaesthesia, and in deep narcosis the main stimulus to respiration is the action of hypoxia on the carotid sinus. Thiobarbiturates increase the sensitivity of the laryngeal and bronchial reflexes, but do not cause laryngeal spasm or bronchospasm in the absence of predisposing factors. Foetal respiration is particularly sensitive to the thiobarbiturates.

In therapeutic doses thiobarbiturates have no effect on uterine tone, but deep anaesthesia depresses uterine musculature. Thiopentone has no effect on Fallopian tube motility. There is a delay of about 5 minutes in the maximum placental transmission of thiobarbiturates.

Large doses of thiopentone result in a depression of liver function for at least 3 days after the administration. The effect of the drug on renal function has not been studied in detail. Thiopentone causes a mild hypoglycaemia and depresses glycogenesis.

Therapeutic doses of thiobarbiturates have no effect on intestinal motility but with their rapid injection there is a marked loss of tone and cessation of movement. Thiobarbiturates have a weak curarising action which is of no clinical significance in normal patients. Although these drugs cause haemodilution and dilatation of the spleen in animals, this effect is minimal in man.

The relative potentcy of four thiobarbiturates is discussed.

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CHAPTER V

VARIATIONS IN RESPONSE TO THIOBARBITURATES

THERE are two guiding principles which are essential for the safe administration of any anaesthetic, (*a*) there is no dose of narcotic which will suit all patients, and (*b*) the least amount of narcotic compatible with the surgical requirements should be used. By appreciating and applying these principles in anaesthetic practice, the modern anaesthetist has done much to reduce the mortality and morbidity associated with the production of narcosis.

Since the inhalation agents are almost all exhaled unchanged, and since their administration and the onset of narcotic effects is a gradual process, it is comparatively easy to relate the dose to the patient's requirements Furthermore, these drugs can be removed rapidly from the body by effective artificial ventilation This does not apply to the intravenous thiobarbiturates, and one of their dangers lies in the fact that an injected dose can only be eliminated from the body by the slow process of detoxication and excretion For these reasons it is more difficult to adjust the dose of thiobarbiturates to the patient's requirements. Fortunately the effective concentration is usually rapidly reduced by diffusion and distribution to the non nervous tissues

Many pathological factors are known to influence the response to thiobarbiturates, but even in the absence of these there is a wide scatter of dosage in normal subjects. This is demonstrated by the coefficient of variation of the average dose of thiopentone required to produce a desired degree of anaesthesia for a given time in several series of normal patients studied by the author (Table XXXVI) The range of dosage in the patients studied varied from 0·24 to 3·9 times the mean dose, but in each series the distribution of dosage on either side of the mean was fairly symmetrical. This wide scatter of dosage applies also to the other thiobarbiturates in clinical use.

VARIATIONS IN HEALTHY SUBJECTS

The author (1954) has investigated the effect of body weight,

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CHAPTER V

VARIATIONS IN RESPONSE TO THIOBARBITURATES

THERE are two guiding principles which are essential for the safe administration of any anaesthetic (*a*) there is no dose of narcotic which will suit all patients, and (*b*) the least amount of narcotic compatible with the surgical requirements should be used By appreciating and applying these principles in anaesthetic practice the modern anaesthetist has done much to reduce the mortality and morbidity associated with the production of narcosis.

Since the inhalation agents are almost all exhaled unchanged, and since their administration and the onset of narcotic effects is a gradual process, it is comparatively easy to relate the dose to the patient's requirements Furthermore, these drugs can be removed rapidly from the body by effective artificial ventilation. This does not apply to the intravenous thiobarbiturates and one of their dangers lies in the fact that an injected dose can only be eliminated from the body by the slow process of detoxication and excretion For these reasons it is more difficult to adjust the dose of thiobarbiturates to the patient's requirements Fortunately the effective concentration is usually rapidly reduced by diffusion and distribution to the non nervous tissues.

Many pathological factors are known to influence the response to thiobarbiturates, but even in the absence of these there is a wide scatter of dosage in normal subjects. This is demonstrated by the coefficient of variation of the average dose of thiopentone required to produce a desired degree of anaesthesia for a given time in several series of normal patients studied by the author (Table XXXVI) The range of dosage in the patients studied varied from 0·24 to 3·9 times the mean dose, but in each series the distribution of dosage on either side of the mean was fairly symmetrical. This wide scatter of dosage applies also to the other thiobarbiturates in clinical use

VARIATIONS IN HEALTHY SUBJECTS

The author (1954) has investigated the effect of body weight

TABLE XXXVI

Coefficient of variation of the average dose of thiopentone administered to produce a desired level of narcosis for a stated time in several series of normal patients described in the literature

Operations	*Anaesthetics used in combination with Thiopentone*	*No. of Cases*	*Period of Anaesthesia*	*Coefficient of Variation of Average Dose*	*Reference*
Abdominal	N_2O-O_2 (50%)-relaxant controlled or non-controlled respiration	121	Induction	36·7	A
			15 mins.	23·0	
			30 mins.	9·8	
			60 mins.	38·6	
			120 mins.	19·3	
		100	120 mins.	29·0	B
Abdominal	N_2O-O_2 (50%)-*d*-tubocurarine chloride controlled respiration	100			C
	N_2O-O_2 (50%)-*d* tubocurarine chloride aided or spontaneous respiration	151	Induction	16·0	
			60 mins.	23·1	
			90 mins.	25·2	
			120 mins.	25·2	
			120 mins.	25·2	
Abdominal	N_2O-O_2 (50%)-relaxant controlled respiration	249	60 mins.	19·3	D
			90 mins.	27·0	
Thoracic	N_2O-O_2 (50%)-relaxant controlled respiration	35	Induction	25·4	
Prostatectomy	Spinal	48	15 mins.	40·0	
			45 mins.	24·3	
			60 mins.	13·1	
			75 mins.	26·1	
Varicose vein ligation	N_2O-O_2 (6/2 litres/min.)	40	Induction	49·0	E
			15 mins.	14·0	
			30 mins.	22·1	
			45 mins.	12·3	
			60 mins.	9·8	
Various non-abdominal	—	40	Induction	27·8	
	Thiamylal (No thiopentone)		60 mins.	4·3	

References.—A Dundee ([illegible]) B Dundee ([illegible]) C Dundee ([illegible]) D Dundee and Richards ([illegible])

sex and age on the dosage of thiopentone in 500 adult patients undergoing abdominal and thoracic operations.

Body Weight This plays a part in determining the dosage of thiopentone, but the relationship is by no means striking and it only becomes very obvious at the extremes of weight The

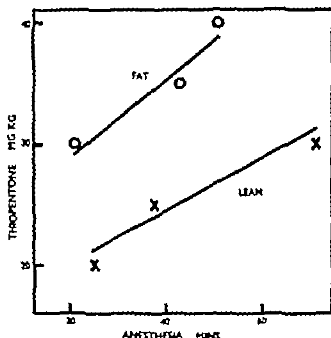


FIG. 28.—Relationship between duration of anaesthesia and dosage of thiopentone in fat and lean rats.
(Hermann & Wood 1952)

volume of circulating blood and the efficiency of the detoxicating mechanisms are factors which participate in limiting the duration of thiopentone narcosis In healthy subjects the blood volume and the size of the liver and kidneys are proportional to the body weight, but this does not apply to the amount of body fat, which is probably a more important factor Hermann and Wood (1952) have found that a 5 per cent. decrease in body fat of the rat resulted in a 100 per cent. increase in the length of anaesthesia with a fixed dosage of thiopentone or in a 40 per cent. decrease in the amount of thiopentone required for a given duration of anaesthesia (Fig 28) Stavinoha and Davis (1955) have also found that the *prior* feeding of the rat on fat, in the form of corn oil, reduced the average duration of thiamylal narcosis (25 mg /kg) from 23 1 to 14 5 minutes.

Sex. In the study referred to above it was found that males required more thiopentone than females to produce a comparable duration of anaesthesia. The studies of Buchel (1954) show that the activity of the sex glands influence the sensitivity of rats to various barbiturates and thiobarbiturates. In the pre-puberty

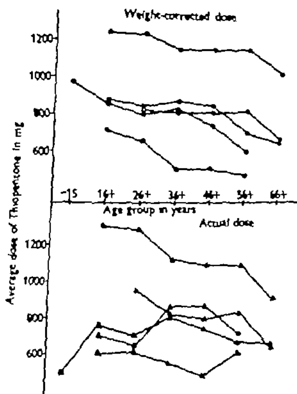


FIG 29.—Relationship of the average dose of thiopentone required to produce anaesthesia for two hours in 5 series of patients and the age of these subjects.
Weight corrected dose—dose in mg./kg.×63
(Dundee, 1954)

stage no difference in response was found between the sexes, but in adults the females slept longer following a given dose than males. Castration of the adult rat prolonged sleep in males but not in females. Treating normal or ovariectomised females with testosterone shortened the duration of narcosis while the administration of oestrogens to normal or castrated males prolonged the sleeping time.

Age. When the average dose of thiopentone in the above series

was calculated on a weight basis, it was found that patients aged 25 years and under required more narcotic than those during middle life and that the dosage declined in patients over the age of 46 (Fig 29). This relationship is not as obvious when the actual requirements of thiopentone are plotted against age The metabolic rate and reflex irritability are increased between birth and 20 years of age, decreasing gradually until the age of 80 (Guedel, 1943) This could partly account for the increased requirements of thiopentone in young persons, since such patients not only detoxicate the drug at a more rapid rate than adults, but more is required to obtund reflex activity The sensitivity observed in healthy elderly subjects can be attributed to the presence of minor undetected degrees of metabolic upset and the decrease in the amount of body fat, both of which are more common in the aged.

ACUTE TOLERANCE

Fig 30 shows the wide scatter of blood thiopentone levels at which 110 unselected fit patients, undergoing minor operations awakened from anaesthesia. The subjects varied widely in age, but all were anaesthetised with thiopentone/nitrous oxide/oxygen and no narcotic was given as premedication. So that the blood concentrations measured in these patients were the ones at which they recovered from the effects of the thiopentone, and not from the combined effects of this drug and nitrous oxide, no patient was included in whom consciousness was gained within five minutes of withdrawal of the inhalation agents. Although the exact moment of return of consciousness is hard to define, this alone is not sufficient to explain the wide scatter of readings as shown in Fig. 30

Acute tolerance to thiopentone has been discussed on page 57, Table XIX, showing that the plasma thiopentone level at the time of orientation is significantly lower following a small dose of thiopentone than the corresponding levels following a large dose. This may be part of but is not the complete explanation of the variations shown in Fig 30 In unpublished observations, the author has been able to relate the blood thiopentone level at the time of orientation with the induction dose of the drug, if there is a not a large variation in the total dose administered. With a

constant induction dose, and a widely varying total dose, the blood thiopentone concentration at the time of recovery increases with the total dose, but the relationship is not nearly as striking as in the first observation. During continuous infusion of dilute solutions of thiopentone, blood concentrations of the drug during

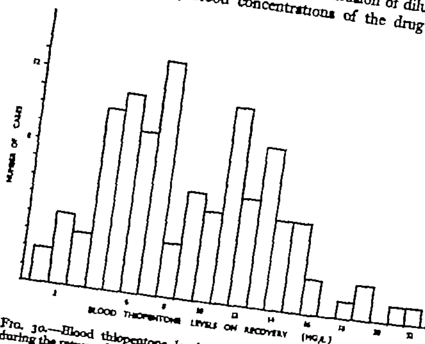


FIG. 30.—Blood thiopentone levels observed in 110 unselected patients during the return of consciousness. Recovery was taken as ability of subject to open the eyes on command.

narcosis have, on occasions, been lower than the level at which the patients subsequently gained consciousness. This only applied when there was a long time interval—with the administration of a large amount of thiopentone—between the withdrawal of the first blood sample and the return of consciousness.

These data show that the blood (or plasma) concentration of thiopentone is not a reliable guide to the depth of narcosis It suggests that the nervous system rapidly acquires tolerance to the drug It would appear that the peak level of thiopentone attained in the plasma (and hence the maximum concentration of the drug in the cerebrospinal fluid and the brain) is the principal factor in determining the blood level at which recovery from thiopentone will occur With the short administration of a small dose of the drug this peak is likely to be attained during the induction period,

while in the prolonged intermittent administrations of large doses the maximum blood level may occur following the injection of a supplementary dose

Studies of thiopentone requirements during surgical anaesthesia support the above hypothesis In unpublished data the author has found that a series of patients in whom anaesthesia was induced with 3 4 mg /kg thiopentone required, on the average, half the amount of the drug to maintain narcosis for 60 minutes than a comparable series of patients in whom the initial dose of thiopentone was between 6 and 8 mg /kg

PATHOLOGICAL FACTORS INFLUENCING THE RESPONSE TO THIOBARBITURATES

RESISTANCE. The term resistance is used here to refer to a state analagous to acquired tolerance to narcotics. Seevers (1954) has defined this as the partial or complete resistance or immunity to quantities of these substances which would otherwise diminish or completely abolish the functional activity of certain neurophysiological and other mechanisms The occurrence of resistance to the effects of thiobarbiturates on the nervous system does not imply that the body as a whole is resistant to the drugs. On the contrary some of the factors which induce resistance to thiobarbiturates may affect organs such as the liver or myocardium and render these more sensitive to the drugs.

The repeated administration of medium-acting barbiturates leads to the development of tolerance to their narcotic effects This has been shown to apply to amylobarbitone and isopropyl β bromallyl barbiturate in rabbits (Fitch, 1930) and delvinal and pentobarbitone in guinea-pigs (Carmichael, 1941) and rats (Carmichael 1948) The above workers, and Gruber and Keyser (1946), have convincingly shown that tolerance to one barbiturate produces a cross-tolerance to other drugs of the same series. Mice develop a tolerance to the daily administration of thiopentone. This effect is maximal in 5 to 6 days and amounts to a decrease in sleeping time by about 50 per cent. (Hubbard and Goldbaum, 1949). Thrice-weekly administrations of thiopentone to the dog lead to a 40 per cent. decrease in the duration of sleep by the end of the third week (Dundee, 1953) Green and Koppanyi (1944) found that dogs rendered tolerant to thiopentone showed cross-

tolerance to hexobarbitone and *vice versa*. The author has verified this with thiopentone, thialbarbitone, thiamylal and hexobarbitone.

TABLE XXXVII

Average duration of narcosis from repeated intraperitoneal injections of thialbarbitone in 20 rats

Results are compared with findings of Green and Koppanyi (1944), who administered repeated doses of thiopentone and hexobarbitone to dogs. No cumulative effects were observed with the latter drugs, given at 24-hour intervals, because the doses of these drugs administered were only about half the potency of the doses of thialbarbitone.

Day of Experiment	*Rats*		*Dogs* (Green and Koppanyi, 1944)	
	Thialbarbitone 60 mg./kg		*Thiopentone 20 mg./kg*	*Hexobarbitone 30 mg./kg*
	Interval from Previous Injection	*Mean Sleeping-time*	*Mean Sleeping time*	*Mean Sleeping-time*
	hrs.	mins.	mins.	mins.
1	—	10·7	95	57
2	20	22·0*	76	—
3	—	—	—	46
4	48	6·2	—	—
5	30	8·5*	32	40
6	24	22·0	31	—
7	—	—	25	59
8	48	6·0	31	—
9	—	—	—	38
10	48	6·0	31	—
11	28	7·0	—	41
12	22	7·5*	—	—
14	48	4·0	—	44
16	48	1·7	—	28
18	48	2·5	—	23
19	—	—	—	36
20	48	1·5	75	9
21	28	10·0*	—	—
22	—	—	—	25
23	48	1·0	—	19
24	24	6·0	—	18
25	24	5·5*	—	13
26	—	—	—	15
27	—	—	—	16
29	—	—	—	13
32	168	10·0	—	—
34	—	—	—	14
36	—	—	—	—
42	240	14·0	—	—

* A cumulative effect was observed because the interval between injections was less than 30 hours.

Tolerance to thialbarbitone occurs in the rat after 6 to 8 injections of the drug at intervals of 24 to 48 hours. However, when the time between administrations is less than 30 hours a cumulative effect is observed. This applies even after 12 injections, when the duration of narcosis is reduced to less than one-fifth of that produced by the first dose of thialbarbitone (Table XXXVII). The tolerance appears to be completely lost when the administrations have been stopped for 7 to 10 days.

Experiments carried out by the author (1955) in dogs and rats show that the repeated administrations of increasing doses of various narcotics and analgesics reduces the duration of sleep with thiobarbiturates. This action is not specific to any one type of drug and occurs also with various antihistamines and chlorpromazine. It is most marked with the opiates and the powerful synthetic analgesics (Fig 31) and least with the antihistamines. Resistance to thiobarbiturates disappears rapidly when the daily administration of narcotics is stopped, and within seven days of their cessation the sleeping time has practically returned to normal.

Marked resistance to thiobarbiturates is rarely encountered in routine anaesthetic practice. Out of over 14,000 detailed records of the administrations of thiopentone studied by the author there were only four instances of marked resistance to the drug. Two of these occurred in a series of about 800 administrations for neurosurgical operations and only two were encountered in the remaining 13,200 anaesthetics. Details of these and other cases collected from various sources are given in Appendix 4. These reports substantiate the experimental evidence that acquired tolerance to analgesic and sedative drugs leads to resistance to thiobarbiturates. This statement must be qualified in the light of cases Nos. 6 and 7 (p 299). Where a large dose of opiate or other drugs has been given to a drug addict immediately before operation, a normal response to the anaesthetic may occur. Chronic alcoholism and hashish addiction can also lead to resistance to thiobarbiturates. Scott (1953) has described a case in which the administration of 2 g thialbarbitone to a hashish addict resulted in nothing more than drowsiness. Observations on one such patient are recorded on page 300.

Many suggestions have been offered to explain acquired tolerance to narcotics, including an increase in the rate of detoxication

of the drugs, interference with chemical mediators or hormones by repeated doses of narcotics, and enzyme adaptation. None of these hypotheses have been confirmed.

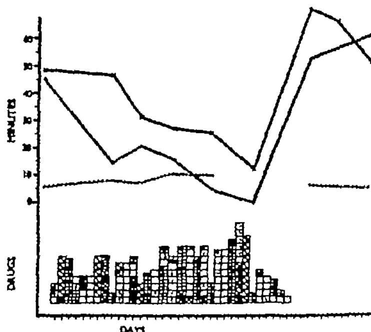


FIG. 31.—The effect of daily doses of various narcotics on the duration of thiobarbiturate narcosis in the dog.

o——o thiopentone 30 mg./kg by intraperitoneal injection.
x——x thiamylal 30 mg./kg. by intraperitoneal injection.
Average onset of narcosis from injection (with both drugs).
Each observation in the average finding with 4 animals.

NARCOTICS AND ANALGESICS GIVEN DAILY

Morphine ¼ gr (16 mg.)
Amidone 10 mg. (Methadone Physeptone)
Pethidine 100 mg. (Dolantin : Meperidine)
Phenadoxone 10 mg. (Heptalgin)
Levorphan 2 mg (Dromoran)
Dilaudid 1 mg.

Hubbard and Goldbaum (1949) found that mice rendered tolerant to the daily administration of thiopentone awaken at higher tissue levels than do controls. The results in Fig. 31 show that the onset of anaesthesia was delayed after intraperitoneal injection of thiopentone and thiamylal in dogs who had previously received large doses of analgesics or narcotics. These findings suggest that tolerance is an adaptation of the nervous system to higher thiobarbiturate levels.

The narcotic effects of morphine (and similar drugs) have been explained by a combination of the drug with receptors near or on the surface of, the neurone Tolerance consists of a maximal, but never complete, saturation of these receptors comparable to that postulated for tachyphylaxis. Cross-tolerance to drugs with a similar chemical structure can be explained by a similarity of the 'anchoring groups This does not explain cross tolerance between compounds of entirely dissimilar chemical characteristics such as thiobarbiturates and opiates. Seevers (1954) has suggested that the resistance is related to the increase in latent hyperexcitability of the neurone rather than to any specific competitive effect.

While most cases of resistance to thiopentone which occur in clinical practice can be explained by an acquired tolerance to narcotics and analgesics an occasional case of idiopathic" resistance is encountered Swerdlow (1949) has described a patient weighing 150 lb (69 kg) who required 2 5 g thiopentone and 70 mg d tubocurarine chloride for a partial gastrectomy lasting 90 minutes, and there must be similar unrecorded cases. No explanation for these can be offered until there is a fuller understanding of the mode of action of thiobarbiturates on the central nervous system.

SENSITIVITY As resistance has indicated relative immunity to the narcotic effects of thiobarbiturates, so sensitivity is here taken to mean the production and maintenance of narcosis with smaller than average doses or prolonged sleep after the administration of average doses of the drugs. The occurrence of sensitivity to thiobarbiturates is rarely due to a single cause, but the factors involved can be grouped as follows

1 Interference with distribution of the drug to non-nervous tissues.
2. Impaired detoxication.
3 Presence of synergistic drugs in the body
4. Abnormal sensitivity of the cerebral cells.
5 Multiple causes

Interference with Distribution. Rapid diffusion to non-nervous tissues is the main reason for the rapid recovery from small doses of thiobarbiturates. With larger doses, or prolonged intermittent administration, diffusion to the body fat is an important means of removal of the drug from the blood stream. A reduction

of the blood supply to tissues which partake in this redistribution (such as liver kidney or skeletal muscle) will decrease the amount of drug required to produce loss of consciousness or will prolong the duration of action of an induction dose. Such an upset of the peripheral circulation will also delay diffusion to the body fat and reduce the amounts required to maintain anaesthesia by intermittent or continuous administration. The most striking example of this is the sensitivity to thiopentone which occurs in shocked patients (see p 145)

A reduction in the mass of skeletal muscle, or the absence of body fat will decrease the pathways available for redistribution of thiobarbiturates This is met with in extreme emaciation. Tissue depots may already be filled with other drugs prior to the induction of anaesthesia, in which case a smaller than normal dose will produce the desired effect. This will be discussed more fully later

Failure of Detoxication. It is now established that the liver is the main site of breakdown of thiobarbiturates in the body the kidney playing a small part in this process. Despite this there are few reports of delayed recovery in cases with liver damage Miller and Tovell (1940) record prolonged unconsciousness after the administration of thiopentone for a dental extraction to a man with considerable hepatic dysfunction. Macintosh and Bannister (1947) state that a slight prolongation of narcosis occurs after the use of thiopentone in jaundiced patients. The author (1952a) describes the occurrence of 18 to 19 hours sleep after 700 mg thiopentone in a 147 lb (67 kg) man with Weil s disease, and narcosis for over 6 hours following the administration of slightly over half a gramme to a 32 year-old male with infective hepatitis. On the other hand Ruth and his colleagues (1939) found no prolongation of narcosis after the use of thiopentone for a laparotomy in the presence of a massive carcinoma of the liver

Controlled observations of the effect of liver dysfunction on the duration of action of thiobarbiturates have already been discussed (Tables XII to XVI) On closer examination of the effects of chloroform induced dysfunction reported by the author (1952a) it can be seen that time taken for the return of the corneal reflex after induction doses of 400 to 500 mg thiopentone was barely altered by liver damage (Fig 32) In all cases the increase in narcosis after the production of hepatic dysfunction became more marked with each successive dose. Furthermore, for the

first 5 to 10 minutes of anaesthesia, during which time the maximum shift of the drug from plasma to tissues was occurring there was no significant difference in the average amounts of thiopentone required by the subjects before and after the production of liver damage. However, at the end of 30 minutes the average dose of thiopentone required in the presence of hepatic dysfunction was about 300 mg less than when liver function

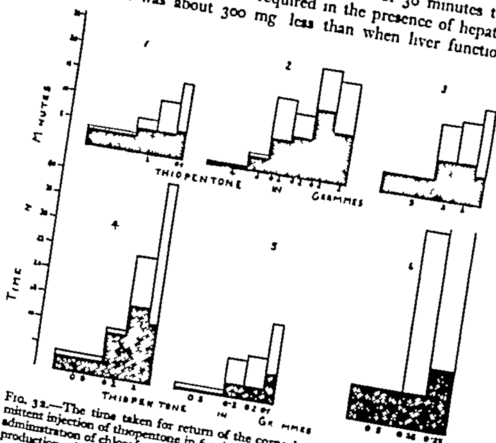


FIG. 32.—The time taken for return of the corneal reflex following intermittent injection of thiopentone in 6 subjects before and 48 hours after the administration of chloroform. The shaded areas show the times before the production of liver dysfunction, the non-shaded areas representing the increases in time at the second administration.
(Dundee 1952a)

was normal. By this time the maximum effects of diffusion would have passed and detoxication would now be playing a major part in the removal of thiopentone from the plasma. These findings show that it is only where large doses of thiopentone are given or when the administration is prolonged, that impairment of detoxication of the drug by the liver will increase narcosis to a degree that can be easily detectable. This is probably why so few cases

of prolonged action of thiobarbiturates in the presence of liv damage have been reported in the literature. Another reason fo the paucity of clinical reports may be that the degree of liver dysfunction must be severe before detoxication is markedly impaired.

The ability of the liver to remove bromosulphalein from the blood stream seems to give the best indication of the state of its detoxicating mechanisms The retention of over 30 per cent. of the dye 5 minutes after the intravenous administration of 2 mg./kg., and 10 per cent. retention 30 mins. after injection, is definitely within the range where the impairment of the breakdown of large doses of thiobarbiturates becomes clinically obvious.

Kidney damage will not be discussed here, as the associated biochemical upset is probably the most important factor in rendering persons sensitive to thiobarbiturates.

A decrease in the rate of detoxication of thiobarbiturates occurs in hypothermic patients as part of the general impairment of body functions which is present at low temperatures. The significance of this cannot fully be appreciated because of the many drugs which are sometimes used as adjuvants in the production of hypothermia and because of the gradual onset of "cold narcosis" Certain reducing systems can prolong the effect of thiopentone in animals, the effect being attributed to prevention of the oxidation to carboxylic acid derivatives This will be discussed more fully later

Synergistic Drugs can induce sensitivity to the thiobarbiturates in three ways.

1 Central Hypnotic Effect. Of the drugs which are synergistic to thiobarbiturates, the most important are the other narcotics. Whilst drugs of the same group may partly block diffusion, their main effect must be on the narcotic-sensitive enzymes of the brain, interference with which leads to the production of anaesthesia. This mechanism also applies to narcotics of different chemical structure, as there is no evidence to show that such drugs produce anaesthesia by other means. The most important synergistic narcotics in clinical use are the opiates, hyoscine, ethyl alcohol, bromides, chloral hydrate, paraldehyde bromethol the phenothiazine derivatives and methylpentynol.

Sub-narcotic doses of the above drugs can together with sub-narcotic doses of a thiobarbiturate, produce anaesthesia. Experi-

ences with the administration of medium acting barbiturates after alcohol suggest that more than a simple summation of narcotic effects can occur. The depression of respiration and of the cardiovascular system is additive and the administration of a combination of less than half the lethal dose of each drug can prove fatal. This is also seen when thiobarbiturates are administered after bromethol or large doses of opiates and dangerous sequelae may ensue. The phenothiazine derivatives, promethazine and chlorpromazine, seem to have little effect on respiration, and thiopentone has been safely administered after large doses of these drugs. Clinical doses of morphine, such as ⅙ to ¼ gr (10 to 15 mg.) have little effect on respiration in healthy adults, especially when combined with atropine, and do not markedly increase the dangers of thiobarbiturates.

Animal experiments show that an increase in duration of narcosis with the three thiobarbiturates can occur for as long as 24 hours after the administration of clinical doses of chlorpromazine (Fig. 33). This time interval has not been studied for other narcotics. During an investigation into the potentiation of thiobarbiturates by chlorpromazine, the author accidentally noted that thiamylal was less potentiated than was either thiopentone or thialbarbitone. Not only was the degree of potentiation less marked with thiamylal but the time interval after the chlorpromazine for which a prolongation of narcosis could be detected was less (Table XXXVIII). This observation also applies to pentobarbitone, promethazine and morphine, all of which have less effect on the duration of action of thiamylal than on thiopentone or thialbarbitone. The more rapid breakdown of thiamylal as compared with the other two thiobarbiturates is a possible explanation for this observation which has been partly confirmed in man.

2. Filling of Tissue Depots. This explains the cumulative action which is seen when a dose of thiopentone is given within 30 hours of a previous injection of the drug (Table XI. Figs. 13 and 14). When the patient has gained consciousness, there remains sufficient of the drug in the tissues to interfere with the redistribution of a subsequent dose. Thiamylal appears to be less cumulative than other thiobarbiturates (Fig. 13) and this may be due to its more rapid detoxication with quicker removal from the tissues.

Although Brodie (1952) has shown that pentobarbitone is localised less extensively than thiopentone in the fatty tissues (Table X) part of its potentiating action on thiobarbiturate narcosis may be explained by its presence in the tissue depots.

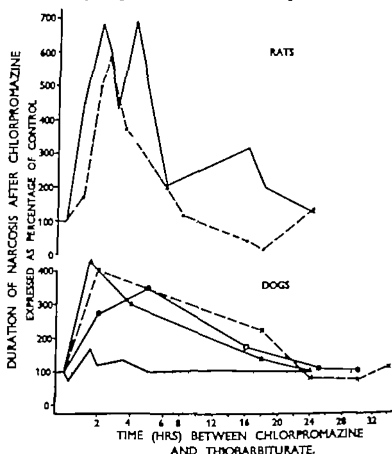


FIG. 33.—Potentiation of thiobarbiturates by the previous intramuscular injection of 2 mg./kg. chlorpromazine in the dog and 4 mg./kg. in the rat.

Rats	——	*thiopentone*	*24 mg./kg*
		thiamylal	21 mg./kg
Dogs	▲—▲	thiopentone	25 mg./kg.
	x—x	thialbarbitone	60 mg./kg.
	o—o	thialbarbitone	50 mg./kg
	——	*thiamylal*	*20 mg./kg*

Thiobarbiturates were given by the intraperitoneal route to rats (see Table XXXVIII) and intravenously to dogs. The average of 6 observations with each drug at each time interval is shown in the case of the dogs.

3 Blocking of Peripheral Stimuli. In discussing the signs and stages of thiopentone anaesthesia the importance of the surgical stimuli at the time of the observation was stressed. By their action

in quantitatively reducing the stimuli reaching the brain, analgesic drugs can potentiate the action of thiobarbiturates. The degree of cerebral depression will be unaltered, but more extensive surgical procedures can be carried out at lighter planes of anaesthesia after the use of analgesics. The most important of these in clinical use are pethidine and levorphan. Some drugs, such as the opiates, combine this action with a sedative effect.

TABLE XXXVIII

Effects of 4 mg/kg chloropromazine given by intramuscular injection, in potentiating narcosis by intraperitoneal injection of equipotent doses of thiopentone and thiamylal in the rat

Drug		*Thiopentone*		*Thiamylal*	
Dose (mg./kg.)		24		21	
Time between Injection of Chlorpromazine and Anaesthetic	*No. of Animals in each Series*	*% Asleep*	*Average Duration of Narcosis*	*% Asleep*	*Average Duration of Narcosis*
hrs.			mins.		mins.
0	96	44	3·8 ± 0·3	40	3·6 ± 0·9
1	32	94	17·0 ± 0·6	57	5·5 ± 0·7
2	26	100	25·9 ± 2·2	92	18·0 ± 2·7
2½	26	92	22·6 ± 2·9	100	22·1 ± 1·6
3	14	86	16·4 ± 3·2	100	14·3 ± 5·3
4	24	83	26·2 ± 2·8	83	12·5 ± 0·8
6	10	100	7·1	75	7·3
8	20	—	—	40	4·3
16	12	75	12·3	25	1·5
18	14	86	7·9 ± 3·3	29	0·5
24	24	60	4·9 ± 1·4	60	4·9 ± 1·0
Overall Average*	—	74	15·5	69	8·1

* Excluding the 8-hour reading (for which there was no observation made with thiopentone) and control observation when no chlorpromazine was given.

The safest combination of drugs which is used to decrease the dosage of thiobarbiturates in clinical anaesthesia is, without doubt, non hypoxic mixtures of nitrous oxide and oxygen. Even with a concentration well below those which produce narcosis marked potentiation of thiopentone occurs (Fig 34). Using a 2:1 mixture of nitrous oxide and oxygen (flow rate not stated) to supplement thiopentone for stripping of varicose veins, Paulson (1952) found the average requirements of the drug in 111 patients to average

14.4 mg./min. of anaesthesia. When nitrous oxide was omitted, the average requirements were of 21·7 mg./min. With flows of 1 litre of nitrous oxide and 1 litre of oxygen per minute, a narcotic concentration of nitrous oxide in the blood (approximately 20 volumes per 100 ml.) is not reached for 40 to 50 minutes, but this

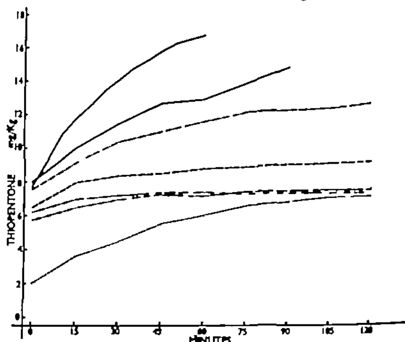


FIG. 34.—Effect of varying concentrations of nitrous oxide and oxygen on dose of thiopentone.

—— Thiopentone used alone to produce narcosis. Upper curve: average requirements of 40 non-abdominal cases.
Lower curve: average requirements of 35 cases in which drug was used to supplement spinal analgesia.

Remainder of figures refer to 4 comparable series of abdominal cases anaesthetised with thiopentone/relaxant/nitrous oxide/oxygen; manually controlled respiration.

— — 1 litre nitrous oxide and 1 litre oxygen per minute.
—.— 2 " " "
— — 3 " "
—·—— 1 litre nitrous oxide and 1 litre oxygen per minute, supplemented by intravenous pethidine.
average dose of pethidine.
(Dundee and Richardson, unpublished observations)

time is reduced to 10 minutes with a mixture of 2 litres of nitrous oxide to 1 litre of oxygen per minute (Gray 1954). Nitrous oxide in a 50 per cent. concentration also possesses greater ability to depress reflexes of autonomic origin than 1 mg./kg. pethidine.)

Although it has been stated previously that muscle relaxants do not increase the duration of narcosis with thiopentone nevertheless they merit inclusion under the heading of synergistic drugs, since they permit surgical procedures to be carried out at a lighter plane of thiobarbiturate narcosis. Reflex somatic response to stimuli is blocked at the motor end plate, although if the depth of anaesthesia becomes too light, reflexes of autonomic origin may result in hypotension, due to vaso-vagal syncope. Prime and Gray (1952) have recorded a fall in cardiac output and a marked rise in the forearm blood flow during such an attack. The time for the ultimate return of consciousness after thiobarbiturates is not prolonged by relaxants, but several factors which are frequently associated with their use may prolong the sleeping time. These include controlled respiration the use of nitrous oxide-oxygen to inflate the patients and sometimes the "minimal' doses of ether frequently used to reinforce the relaxant for peritoneal closure which may be greater than imagined.

There are many drugs synergistic to thiobarbiturates which are of academic interest only Although, strictly speaking they should be included in this section for the sake of simplicity all agents which at the present time have no clinical application will be grouped together and discussed later (p 139)

Abnormal Sensitivity of Cerebral Cells. Under this heading all narcotic drugs already discussed in the previous section are applicable since where there is already some interference with the narcotic sensitive enzymes of the brain, correspondingly smaller amounts of thiobarbiturates will be required to extend this interference to an extent which will result in anaesthesia.

Bain (1952) has noted that barbiturate anaesthesia in rats and mice was potentiated by dinitrophenol (D.N P). There is a close resemblance between the *in vitro* dissociating effects of D.N.P and thiobarbiturates on oxidative and phosphorylating processes in liver and brain mitochondria (Brody & Bain, 1954) Since the widely used agricultural herbicides dinitro-*ortho*-cresol (D N C.) and dinitro-*sec* butylphenol (D.N B P dinoseb) have a mode of toxic action almost indistinguishable from that of D N P Edson & Carey (1955) investigated the response of normal and D.N C -poisoned animals to six barbiturates including thiopentone, thialbarbitone and hexobarbitone With the exception of hexobarbitone, the narcotic effect of the barbiturates tested

was markedly potentiated by the presence of severe D.N.C. intoxication. Deeply anaesthetising, but normally non fatal doses of both thiopentone and thialbarbitone were lethal in D.N.C. poisoned rats. Most such animals developed deep cyanosis within seconds of the intravenous injection of the thiobarbiturate and died immediately or within a few minutes after respiratory and then cardiac arrest. The failure of D.N.C. to potentiate hexobarbitone was explained on the grounds that this barbiturate causes appreciably less *in vitro* dissociative effect upon mitochondrial oxidative phosphorylating processes than the others which were studied.

The results of Edson and Carey (1955) suggest that barbiturate potentiation is only likely to occur with D.N.C. dosages high enough to cause characteristic signs of poisoning and profound disturbances of cellular oxidation phosphorylation processes. Low D.N.C. dosage did not appear to potentiate high thiopentone dosage, whereas high D.N.C. dosage potentiated even quite low thiopentone dosage.

Thiobarbiturates are recommended for the control of those convulsions which occasionally follow the administration of local analgesics. *Prolonged narcosis, even when only small doses of thiopentone have been used for this purpose, has been described* by many workers. Rees and Wakeley (1949) describe a case in which 125 mg thiopentone were used to control convulsions after topical application of amethocaine. Aided respirations was required for 10 minutes and the patient did not react to supra orbital pressure until 30 minutes after the thiopentone. In another patient to whom 500 mg thiopentone were given to control convulsions following 3 ml. 10 per cent. cocaine, Wilson (1949) states that artificial respiration was required for 30 minutes. The author has encountered 120 minutes of deep anaesthesia following 300 mg thiopentone used, to control convulsions due to the topical application of 200 mg amethocaine.

Although the aetiological factors have been extensively studied, *the exact mechanism of the production of convulsions by the local analgesics* is not known. Harris (1951) states that it is probable that any factor which effects the rapid release and/or the accumulation of acetylcholine at central synapses may produce stimulation of multitudes of such synapses and the firing off of a large number of central motor neuroses leading to a generalised con-

vulsion If this hypothesis is correct, the prolonged narcosis from thiobarbiturates (which occurs under these conditions) may be somehow related to increased sensitivity of cerebral cells, since the rapid release of acetylcholine may be a factor in the production of narcosis.

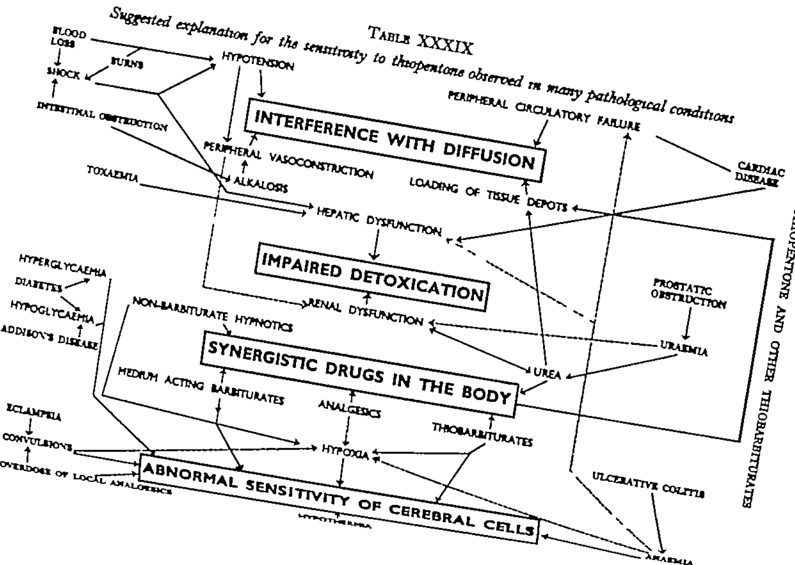
The so-called glucose effect' of certain drugs, to be discussed later, has been attributed to a decrease in the permeability of the blood-brain barrier At the present time this is only of academic interest. Part of the increased sensitivity to thiobarbiturates which occurs at low body temperatures can also come under this heading The multiplicity of factors involved in this sensitivity has already been mentioned

Multiple Causes for Sensitivity It is rare to find a patient, who has slept for a long time after a small dose of thiobarbiturate, or in whom anaesthesia has been induced with what are generally agreed to be sub-narcotic doses of the drugs, in whom only one possible explanation can be found for this sensitivity An attempted explanation for the various clinical states in which sensitivity to thiobarbiturates have been observed, for which more than one aetiological factor can be incriminated is given in Table XXXIX. Since in most of these conditions sensitivity is not limited to the narcotic effects of the thiobarbiturates, and special care is required for safe administration, this will be discussed in detail in the next chapter An exception is made in the case of the sensitivity to thiopentone which has been observed in anaemic and uraemic patients and which, in the lack of a better explanation, will be discussed under the present heading

The author (1952c) has studied the duration of anaesthesia with a single 500-mg dose of thiopentone in 253 male patients undergoing cystoscopy and 260 female patients having a cervical dilatation and curettage. *On relating the results to the haemoglobin* content (Haldane standard) of the blood, it can be seen (Fig 35) that anaesthesia was more prolonged in anaemic patients. Even allowing for the 10 per cent. error which is attributed to the dilution methods for determining the haemoglobin there is a significant ($p < \cdot 001$) increase in narcosis in subjects with values between 8 and 9 g per cent. as compared with the 12 to 13 g per cent. haemoglobin group This investigation has also been carried out on a series of patients using a dose of thiopentone which is related to body weight, with similar results to the above. Six observations were made in one patient who underwent

TABLE XXXIX

Suggested explanation for the sensitivity to thiopentone observed in many pathological conditions



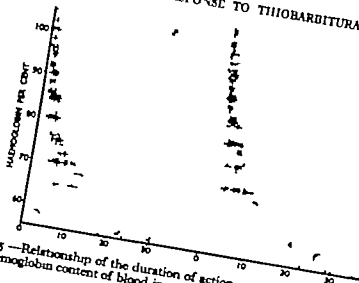


FIG. 35 —Relationship of the duration of action 500 mg of thiopentone to the haemoglobin content of blood in 2 series of cases referred to in the text. (Dundee 1952c)

repeated cystoscopic examinations at varying haemoglobin levels. Again an increased duration of anaesthesia was encountered in severe anaemia (Fig 36)

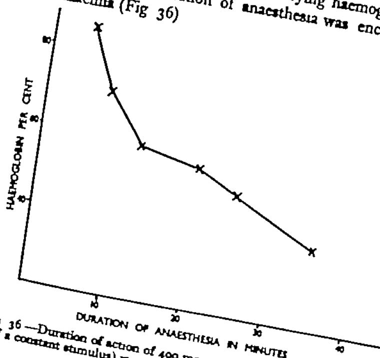


FIG 36 —Duration of action of 400 mg of thiopentone (in the presence of a constant stimulus) in one patient at various haemoglobin levels. (Dundee 1952c)

It is difficult to offer a satisfactory explanation for this prolongation of thiopentone narcosis in anaemia. Liver dysfunction

is a common finding in this condition. Bomford and Rhoades (1941) in a study of severe refractory anaemia, found varying degrees of liver damage in all of the 24 autopsies they reported. This is not likely to play a major part in prolonging the narcosis with the small doses of thiopentone used in the above study. There will be less linking of the drug with erythrocytes, but the part played by this in recovery from thiopentone is not known.

Cerebral cells may become more sensitive to narcotics because of anaemic anoxia. The work of Peterson, Shideman and Linares (1950) supports this latter view. They induced hypoxia in dogs by the administration of an agent (*p*-amino-acetophenone) which is capable of inducing 46 to 78 per cent. methaemoglobin, or by forcing the animals to breathe an atmosphere containing 6 to 7 per cent. oxygen. The resulting hypoxia markedly prolonged the action of thiopentone, the righting reflex returning at plasma barbiturate levels which were 19 to 44 per cent. below the control observations. There was no interference with the plasma thiopentone decay curves showing that the rate of detoxication of the drug was not altered.

The presence of a large amount of urea in the body whether due to ingestion of the drug or in the clinical syndrome of uraemia engenders in patients extreme sensitivity to thiobarbiturates (Dundee & Richards, 1954) and barbiturates (Dundee & Annis, 1955). The increase in duration of narcosis is roughly proportional to the blood urea level (Figs 37 and 38).

It has been mentioned (page 35) that plasma from nephrectomised animals binds thiopentone much less than plasma from normal patients. Since the increase in thiopentone narcosis in nephrectomised animals is not observed until the blood urea increases (Table XVII) the decreased binding ability of plasma from such animals is probably due to the increase in urea and other electrolytes. Sensitivity to thiobarbiturates may thus be due to an increase in the percentage of physiologically active concentration of the drugs which occurs after injection, as compared with normal subjects.

Urea, being one of the most diffusable substances known, exists in abnormal concentrations in the tissues to which thiobarbiturates normally diffuse. This may interfere with distribution of the narcotic to non nervous tissues, with subsequent decrease in the early rapid decline in the plasma concentration. Where uraemia

is due to kidney dysfunction there may be a concomitant reduction in the ability of this organ to detoxicate thiobarbiturates. The kidney does not play a major role in the breakdown of these drugs and this is not the main reason for the sensitivity to thiopentone which occurs in uraemia.

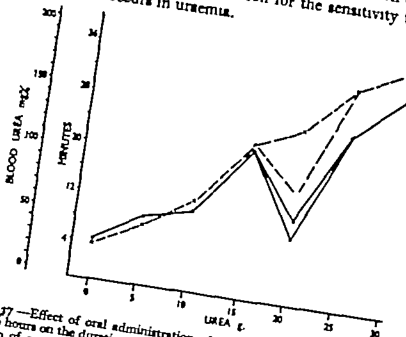


Fig. 37.—Effect of oral administration of urea and deprivation of fluids for 36 hours on the duration of narcosis following the intravenous administration of 20 mg./kg. thiopentone in the dog. The duration of narcosis was measured by the method described by Dundee (1953).
o——o Duration of narcosis. x— —x Blood urea.

Induced Sensitivity of Academic Interest. The following conditions are considered separately lest they should distract from the essentially clinical nature of the above discussion, although most of the factors involved fit into one or other of the classifications which have been already mentioned.

The reinduction of thiobarbiturate anaesthesia by the intraperitoneal injection of 50 per cent. glucose in the guinea pig was first described by Lamson, Greig and Robbins in 1949. On recovery of consciousness, an injection of glucose immediately resulted in a return of deep narcosis. The period of anaesthesia was less than the original but on recovery a second dose of glucose promptly reinduced narcosis. This cycle of going back to sleep with glucose could be repeated several times, but each time the animal slept for a shorter period of time and finally could not be put back to sleep in spite of injecting a very large amount of glucose.

Studies by Lamson *et al.* (1952) with hexobarbitone show that the rate of metabolism of the drug was not affected and that animals were put to sleep for a second time at lower brain concentrations of the drug

than those under which they previously regained consciousness. Some of the substances which caused the "glucose effect" e.g. lactate, pyruvate and glutamate, increased the permeability of the brain to barbiturates, but this did not apply to glucose. Acetylcholine prevented this increased permeability and at the same time prevented the return to sleep both by compounds which affected and those which did

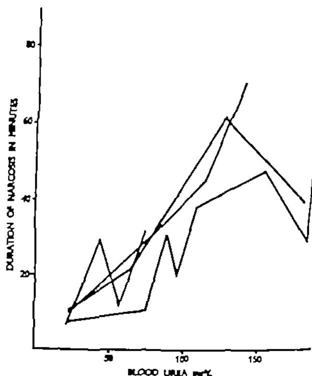


FIG. 38.—Relationship between the blood urea and the duration of thiopentone narcosis in 4 dogs in whom a condition simulating uraemia was induced by vesico-appendicular anastomosis with ligation of the urethra. (Dundee & Annis, 1955)

not affect permeability. Hypertonicity of the solutions was another possible explanation, but again this did not apply to all cases.

Lamson, Greig and Williams (1952) and Lamson and Greig (1953) are of the opinion that adrenaline may be the causative factor in the "glucose effect" irrespective of what drug is used for its production. They base this on the findings that it could be blocked by anti-adrenaline drugs such as benzodioxane, and that the return to sleep produced by lactate and glutamate following barbiturate anaesthesia did not occur in adrenalectomised guinea pigs although in such animals it could be produced by adrenaline. They have not been able to demonstrate any changes in the adrenaline content of peripheral blood after the injection of lactate in dogs, but explain this failure on the grounds that they could not even find an increased blood-adrenaline level five minutes

after the injection of a theoretically detectable amount of the drug No reason is offered for this effect of adrenaline except for the quotation of references relating to its analgesic action and the production of anaesthesia in dogs after the intracisternal injection of large doses.

Richards, Bertcher and Taylor (1952) have studied this problem and added sodium chloride, urea and polyvidone to the list of drugs which will reinduce sleep after recovery from thiopentone. They found no obvious connection between this property and the chemical nature of the solutions. Apart from the possibility of a change in the permeability of the blood brain barrier these workers could offer no explanation why the injection of such drugs should reinduce sleep at falling blood levels of barbiturate and maintain this state at a concentration at which the animals are usually already in a state of recovery

These observations have not been confirmed in man. Although an annotation in the *Lancet* (1950) issued the warning that if the glucose effect occurs in humans, 'caution will have to be exercised in the use of *intravenous glucose drips during barbiturate anaesthesia or in the immediate post-operative period* no cases of this potentiation have been reported to date.

The influence of two redox systems, ascorbic acid-dehydroascorbic acid and cysteine-cystine, on thiopentone anaesthesia in the mouse has been studied by Giarman and Flick (1951). Each of these compounds, when injected prior to the thiopentone, prolonged the anaesthesia, the ascorbic acid dehydroascorbic acid being more potent than the cysteine cystine system. Both ascorbic acid and dehydroascorbic acid are capable of reinducing two to six cycles of anaesthesia after recovery from the initial thiopentone.

Since oxidation plays a major part in the breakdown of thiopentone, it is felt that a large amount of a potent reducing agent, such as ascorbic acid, may interfere with this process. Conversely, the presence of oxidising substances, such as dehydroascorbic acid, might be expected to hasten recovery from anaesthesia. However the oxidising substances referred to above quickly form equilibria with their reducing partners *in vivo* the administration of dehydroascorbic acid resulting in the formation of a large quantity of ascorbic acid at the expense of reduced glutathione. Thus the net effect of administering dehydroascorbic acid to the mouse is that of introducing a source of reducing material, ascorbic acid, which is not produced instantaneously but over a period of time. This view is supported by the finding that dehydroascorbic acid produced more prolongation of thiopentone than its reducing partner ascorbic acid.

The reinduction of anaesthesia suggests that in addition to the above, the mechanism of thiopentone potentiation may involve an effect on the systems associated with the production of narcosis. However as Giarman and Flick pointed out, large quantities of the acids at pH 5·0 to 6·0 were required to produce this reinduction effect, and there is a possibility that the action observed may have been due to an acidotic coma.

Giarman, Flick and White (1951) found that the administration of disulfarim (Antabuse) for three days resulted in a sixty fold increase in the duration of thiopentone anaesthesia in the mouse. Winters, Shideman, Richards and Taylor (1952) could not confirm this finding in the dog or mouse, but found that a single oral dose prolonged thiopentone narcosis in the rat. Giarman *et al.* postulated that the prolongation of narcosis with disulfarim was due to its inhibitory effect on xanthine oxidase and suggested that xanthine oxidase is one enzyme functioning in the breakdown of thiopentone to its carboxylic acid derivators. Winters *et al.*, on the other hand, thought that the prolongation of narcosis in the rat was due to some alteration in the sensitivity of the central nervous system to thiobarbiturates.

Cooper Slocum and Allen (1953) are of the opinion that disulfarim does not increase the dangers of thiopentone narcosis in man, although *it may render patients susceptible to ether and chloroform.*

Frommel (1947) has shown that parasympathetic stimulant drugs such as acetylcholine, potentiate the effect of barbiturates. The resulting vagotonia (' internal acetylcholaemia ') has the same effect as cholinesterase inhibition. It has been suggested that this work demonstrates a vagal component of sleep This potentiation has not been shown to apply to thiobarbiturates. Neostigmine is frequently used at the end of thiobarbiturate anaesthesia to reverse the action of certain muscle relaxants, and there are no clinical reports of delayed recovery following this combination of drugs. Perhaps this may be explained by the neutralisation of the vagal stimulant action of neostigmine by the use of adequate doses of atropine.

Cook, Toner and Fellows (1954) list a large number of drugs which will prolong the action of barbiturates. These include alcohol, cholesterol, antihistamines, histamines, certain nitrates, glycerine, sorbitol and inorganic iodides. Most of these agents increase the sleeping time for periods only one-third to two-thirds greater than was exhibited by animals which received barbiturates alone. These workers have shown that β-diethyl-aminoethyldiphenylpropylacetate hydrochloride (S.K.F 525 A) in single doses caused a 35 fold increase in the action of hexobarbitone in rats, without significantly altering the toxicity of the hypnotic agent. None of the above drugs has been shown to effect narcosis with the thiobarbiturates.

Analysis of Dosage of Thiobarbiturates Reported studies in which the average dose of thiobarbiturate in a number of patients is expressed solely as mg./kg./min. or mg./min. are valueless. Since requirements of narcotic decrease with time, as the tissues become saturated, one cannot compare the amount of drug administered over a ten-minute period with that given during two hours of anaesthesia. The latter figure will not be twelve times the former Average dosage must be expressed as mg (or mg./kg.) per fixed unit of time for all cases. Furthermore, it is wrong to compare the average total dose of a series of patients who were given a small induction dose with those of a similar series who received a large initial dose. It would probably be

of more value to calculate the average ratio of the total dose to the induction dose at a given time, rather than the average total dose if the initial dose is not stated or has a very large scatter. In all of the studies on dosage of thiopentone reported by the author and his colleagues, an attempt has been made to standardise the induction dose on a weight basis.[1] If all factors (such as the age, weight and physical state of the patients, premedication, anaesthetic techniques and the nature of the operations) are comparable save the one under study it is then permissible to compare the average total dose of thiobarbiturate given at any fixed time to two series of patients.

The importance of sensory stimuli in modifying the response to thiobarbiturates has been stressed in the previous chapter. This is of great importance in clinical anaesthesia. In the absence of shock, patients with painful wounds or burns will require much larger doses of drugs to induce a satisfactory degree of narcosis than patients having elective surgical operations. With different operative procedures the increments of thiobarbiturate required during maintenance of anaesthesia will vary with the intensity of the surgical stimuli. For this reason it has been mentioned above that any series of cases whose average requirements of thiobarbiturate can be compared, must be comparable as regards the nature of the operations and if possible, the surgeons should be the same for both series.

SUMMARY

Normal patients vary enormously in their response to thiobarbiturates. The dose of thiopentone required to produce anaesthesia varies with the body weight. The requirements of this drug are decreased in elderly subjects. On the whole, males require more thiopentone than females.

Resistance to the narcotic effects of thiobarbiturates occurs in conjunction with tolerance to any sedative or analgesic drugs and to a lesser extent with antihistamines. Resistance to the narcotic effects does not necessarily imply that the body as a whole will be resistant to the increased requirements of thiobarbiturates.

Sensitivity to thiobarbiturates is induced by any factor which interferes with their diffusion. Of lesser importance is the production of sensitivity is impairment of detoxication. The presence of synergistic drugs in the blood stream may also prolong anaesthesia. Some cases of sensitivity can be attributed to undue sensitivity of cerebral cells.

In a large variety of clinical conditions decreased tolerance to thiobarbiturates is the result of a combination of two or more of the above factors. The duration of action of thiopentone is longer in patients with a low haemoglobin level. This may be due to anaemic hypoxia increasing the sensitivity of the cerebral cells to the drug.

Acquired sensitivity to thiobarbiturates has been induced with many drugs, but most of these observations are solely of academic interest.

[1] The large coefficient of variation of the average induction doses in Table XXXVI is due to the fact that this is calculated from the actual dose and not the dose per unit of weight.

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CHAPTER VI

THE USE OF THIOPENTONE IN CERTAIN PATHOLOGICAL CONDITIONS

IT has been stressed in the previous chapter that sensitivity to thiobarbiturates is not limited either to the production of narcosis with small doses of the drugs or to delayed recovery after what are considered to be normal doses. Systems other than the central nervous system may be unduly susceptible to the depressant effects of thiobarbiturates. In this section most of the pathological conditions in which extreme caution should be exercised in the use of these drugs will be described and precautions for their safe administration discussed.

For the sake of simplicity, in this and succeeding chapters, reference will only be made to the use of thiopentone, except where mention of another drug is specifically warranted The remarks should be taken as applying equally to the use of thiamylal and thialbarbitone, with an appropriate allowance for the difference in potency of these drugs (p 109).

SHOCK

Shock is a vague term which includes many clinical syndromes. It is used here to refer to any condition where there is a marked discrepancy between the volume of the circulating blood and the capacity of the circulatory system. Many workers have pointed out that increased sensitivity to pentobarbitone and to ether and other inhalation agents occurs in the presence of shock, and that great care should be taken to avoid overdosage.

The different responses of normal and shocked patients to intravenous barbiturate anaesthesia is well demonstrated by the morbidity and mortality which occurred when thiopentone and hexobarbitone were administered to the American casualties at Pearl Harbour in 1941 Halford (1943) describes his experiences as follows

"A number of patients were given evipal by competent anaesthetists only to have respiratory failure, some of which ended in death. After

several such fatalities, pentothal sodium was used, and again respiratory failures occurred and, as in the case of evipal, death ensued in enough cases to cause us to abandon it as too dangerous. In several cases when as small an amount as 0 5 g of pentothal sodium solution had been administered, there suddenly appeared a cyanosis decolletage predecessor of death.

Halford points out that the wounded were all healthy young adult males with adequate lung volume and unbelievable morale" He continues,

> The injuries were all severe, the list of wounds consisted mainly of traumatic amputations of one or more extremities often in the same patient, compound comminuted fractures, penetrating chest and abdominal wounds, head and jaw injuries.
>
> That we were attending patients in severe shock there can be no denial. These patients were prepared with perhaps a minimum of plasma and whole blood transfusions. There was a definite lack of oxygen and equipment for administering continuous oxygen therapy "

This report condemns the use of intravenous anaesthesia in the presence of shock, referring to it as an ideal form of euthanasia" No suggestion is made that the technique of administration was at fault, and no part of the blame is put on the *competent* anaesthetists. An editorial appearing in the same issue of *Anesthesiology* (1943) as Halford s paper makes the following pertinent comment

> Direct and indirect information from Pearl Harbour would lead to the belief that administration of both evipal and pentothal sodium to severely wounded casualties is extremely hazardous. Both drugs are said to have produced sudden and often irreversible respiratory failure in a number of cases. While it would be reasonable to assume that these occurrences were directly attributable to the barbiturates, it would be instructive to know more concerning how rapidly and in what amounts the barbiturates were administered and what concentration of solution was employed.

It concludes,

> When pentothal sodium is administered intravenously to patients who are in a state of shock, the lessened tolerance of these patients must be kept in mind. Small doses (1 to 2 cc. of a 2 5 per cent. solution) administered slowly with intervals between injections of sufficient length to allow the full effect to take place, is the only rational scheme of dosage. It is amazing how little of the drug will provide anaesthesia and relaxation for such patients. Oxygen is an important adjunct to many patients in shock who are under intravenous anaesthesia, and when shock is present it should be available for use if required.

The truth of these statements has been borne out by numerous reports from civilian and military anaesthetists all over the world. They emphasise that, when used properly within its limitations thiopentone is a safe drug in the presence of shock. A few extracts from papers contemporary with Halford's illustrate the safe use of thiopentone in the presence of shock.

Adams and Gray (1943) describe in detail anaesthesia successfully administered to a young woman who had attempted to commit suicide by discharging a shot gun into her body

"The charge had entered just below and to the left of her left breast. A portion of the left side of the thorax had been blown away and comminuted fractures of the sixth to ninth ribs had been sustained. The spleen and a portion of the left lung were protruding from the wound of exit. There was a large laceration in the diaphragm, through which all of these intra abdominal structures also protruded. The lower portion of the left lobe of the lung was lacerated."

The patient had received ¼ gr (16 mg) morphia 45 minutes before operation and transfusion consisted of 500 ml. whole blood. Before induction she was restless and only partly coherent, B.P was 80/40 with a pulse rate of 100 per minute.

Anaesthesia was induced with serial doses of 2½ per cent. thiopentone given slowly. After 100 mg the patient was asleep and a further 25 mg permitted easy oral intubation. A mixture of 50 per cent. nitrous oxide/oxygen and intermittent doses of thiopentone were used for maintenance, a total of 400 mg being sufficient for a 90-minute operation. With the aid of blood transfusion her systolic blood pressure was restored to 110-115 mm. Hg

Twenty five days later the same patient (now in a comparatively healthy state) required 400 mg thiopentone during the first ten minutes of the drainage of an empyema.

Marshall (1943) discussing anaesthesia under war time conditions, remarks

"Pentothal was a godsend . . . men for whom we used it were very ill, suffering from burns, sepsis, toxaemia, anaemia, etc., and a small dose went a long way. Pentothal/nitrous oxide/oxygen was excellent for poor-risk cases."

Zentgraf and Eversole (1943) comment that

". . . in military surgery . . . especially under front line conditions, pentothal sodium is an extremely valuable and widely used drug. Its scope has been greatly widened by its use in combination with other methods."

It is definitely established that shock renders a patient more sensitive to thiopentone and other intravenous barbiturates and

indeed to all anaesthetics. Even so it can be safely administered to such subjects. Its danger lies in the ease with which an over dose can be given and the difficulty in resuscitation once this has occurred. Before dealing in detail with the use of thiobarbiturates to shocked patients, it is advisable first to consider some of the reasons for their reduced tolerance, in order to clarify the principles of safe administration.

It must be realised that the sensitivity to thiobarbiturates which exists in patients suffering from shock is not limited to a prolonged narcosis after small doses. Respiratory depression and cardiovascular collapse may result from doses which would have no such effects in normal subjects. More widespread effects, such as liver and kidney dysfunction, may result from the use of small amounts of thiopentone in shock.

In general the events following the administration of half a gramme of thiopentone to a shocked patient are similar to those occurring after two or three times this dose has been injected rapidly into a normal subject. It has been pointed out previously that the distribution of the drug to non nervous tissues is interfered with in shock. This applies to that diffusion which occurs immediately after injection, as well as to the later diffusion of the drug to the fat depots. Compensatory mechanisms, including peripheral arteriolar constriction, endeavour to relate the capacity of the peripheral vascular bed to the available circulating blood volume thereby maintaining the systemic blood pressure. The cardiac output increases, although the output per beat usually falls, and return of the blood to the heart is assisted by the constriction of the peripheral veins. This generalised constriction of peripheral vessels diverts the thiopentone from its normal pathways of diffusion.

Whereas, under normal conditions, the plasma concentration of thiopentone falls to less than 25 per cent. of its peak level within 15 minutes of injection, in shock this reduction will be much less and a desired effect can be produced by smaller amounts of the drug. Reliance is thus placed more on detoxication than on diffusion for the removal of thiopentone from the blood stream, and this is a slow process, even in fit subjects. Hugill (1950) reports that in moderate degrees of shock the portal blood flow is reduced by about half. Davison, Lewis Tagnon and Adams (1946) and others have drawn attention to the deleterious effects

of hypotension with the resulting hypoxia on hepatic function The renal circulation is known to be particularly sensitive to changes in the blood pressure and renal vasoconstriction may persist for long after the blood pressure has been restored to normal These factors lead to a reduction in the rate of break down of thiopentone and in resulting prolongation of its action

In a state of shock, patients appear to be less aware of pain Since the clinical level of narcosis is related to the intensity of stimulation reaching the central nervous system and attempting to overcome the depressant effects of thiobarbiturates, shocked patients may fall asleep at lower plasma levels of the drugs than do normal subjects After prolonged hypotension the cerebral cells themselves may be more susceptible to the effects of depres sant drugs. These are additional factors which may play a part in prolonging narcosis in shock and which also reduce the dose of thiopentone required to induce sleep

Clinical reports have shown that a damaged myocardium is more susceptible to the depressant effects of thiopentone than is the normal heart muscle. In shock, the haemoconcentration increases the work of the heart, there may be reduced efficiency due to compensatory tachycardia and if the systemic blood pressure is low, the coronary circulation will be decreased. These factors combine to reduce the healthy heart to a state analogous to that induced by disease. Moreover not only is the heart muscle thus made more susceptible to thiobarbiturates but it remains in contact with a high concentration of the drug for a longer period of time.

It is important to remember the vasodilating properties of moderate doses of thiobarbiturates In acute depletion of the blood volume an adequate systemic blood pressure is only main tained by intense vasoconstriction, should this latter be broken by thiopentone, a critical degree of circulatory failure will ensue. A vicious circle is thus set up The blood pressure falls and the degree of myocardial hypoxia is increased, leading in turn to further hypotension Capillary permeability is increased, deplet- ing the circulating blood volume even more and increasing haemoconcentration. Unless energetic resuscitation is carried out, the stage of irreversible shock will be reached. Varying degrees of this picture can occur depending on the severity of the shock, the dose and rate of administration of thiopentone, and

the general condition of the patient when in normal health. Even in the less severe degrees of shock, when the thiopentone injection does not result in a marked hypotension, the effects on the renal and hepatic circulations may affect the ultimate outcome.

The deleterious effect of thiopentone on the cardiovascular system is paralleled by its effects on the respiratory system. Depression of respiration, or even apnoea, follows the administration of small doses to shocked patients. There may be a true sensitivity of the respiratory centres resulting from prolonged hypoxia, either the result of arterial hypotension or due to an increased intracranial pressure following injury to the head. The stimulating effects of carbon dioxide will be very much reduced or even completely abolished.

The classical first aid treatment of shock consists of among other things, the subcutaneous injection of opiates. Their absorption is grossly impaired by the reduced skin blood flow and the absence of the clinical effect within the expected time may lead to a repeat injection. This large dose will be released rapidly into the general circulation when the vasoconstriction is overcome. Should this happen soon after the induction of anaesthesia, thiopentone is likely to be blamed for the reduction in the respiratory minute volume. Respiratory depression increases tissue hypoxia, and unless artificial respiration is carried out, another vicious circle will be set up

Mechanical interference with the peripheral mechanism of respiration as a result of trauma presents a problem irrespective of the anaesthetic agent used. This also applies to obstruction of the tracheo-bronchial tree by blood, foreign bodies or gastro-intestinal contents. It must be remembered that shock and opiates both retard digestion, motility and absorption in the alimentary tract. In traumatic shock it is more important to know the time interval between the last meal and the accident, than the time between the last meal and the induction of anaesthesia. Failure to appreciate this has led to many fatalities. This problem of regurgitation of gastro-intestinal contents following induction of anaesthesia is later discussed in detail.

A less frequent but none the less serious difficulty in the administration of thiopentone to shocked patients arises from the lack of suitable veins. The irritant effect of the subcutaneous injection of the drug may be more marked on tissues which are

partly depleted of their blood supply If no brachial pulse is palpable, it is easy to inject the solution into an artery, especially since all the recognised signs of this catastrophe may be absent. Aspiration may reveal venous-looking blood, the patient may not complain of pain following the injection and a delay in the onset of sleep could be attributed to the sluggish circulation A more obvious explanation will almost certainly be looked for to explain the non return of the radial pulse.

The experiences of Brittain and Latter (1940) with air raid casualties have shown that only in a few shocked cases does early operation save life. If circumstances permit, resuscitation should be carried out before the induction of anaesthesia. Blood loss is preferably replaced by whole blood transfusion, but if supplies are not available the blood volume should be increased by the use of plasma or synthetic plasma substitutes (dextran, polyvidone) *L*-noradrenaline is often of value in certain cases (Shanahan, 1955). Generalised heating should be avoided, although the application of local heat to a limb is a valuable aid when setting up an intravenous infusion.

Intravenous administrations of premedication is preferred in shocked patients, for reasons already given. Both atropine and opiates should be used sparingly or even omitted, the former because it causes tachycardia and the latter because of its depressant effects on respiration. If a subcutaneous injection of morphine or another opiate has been given since the onset of shock, it is best to limit premedication to small doses of atropine. The intravenous use of pethidine is not without danger as it causes tachycardia, and cardiovascular collapse has followed its use.

The inhalation of oxygen for 5 to 10 minutes before the induction of anaesthesia is a great help By starting off with the lungs full of oxygen, a longer period of respiratory depression or obstruction can occur before the onset of hypoxaemia. The removal of part of the alveolar nitrogen makes a subsequent administration of nitrous oxide/oxygen mixtures more quickly effective.

If there is any suspicion of a full stomach, ideally a large-bore stomach tube should be passed and aspiration performed. The unpleasantness of passing this in a conscious patient can be reduced by liberally lubricating the tongue with liquid paraffin or glycerine, whilst having a needle in a vein and commencing the injection of thiopentone at the same time as the tube is passed

With this technique the author (1950) found that over 60 per cent. of patients did not remember the passage of the stomach tube unfortunately this procedure cannot be carried out single handed. Alternative methods of anaesthesia in the presence of a full stomach are discussed in the section dealing with acute intestinal obstruction.

Thiopentone should be prepared in a very dilute (2 to 2 5 per cent.) solution for the induction of anaesthesia in shocked patients. The injection should be given slowly in doses of 20 to 50 mg with a pause of at least thirty seconds between successive doses in order to allow their full effect to be observed before a further dose. The use of a dilute solution and a narrow-bore needle is a safe-guard against too rapid injection, e.g if the full contents of a 10-ml. syringe of 2 per cent. solution (200 mg) are injected over a minute by an inexperienced anaesthetist, much less harm will result than if a 5 per cent. solution (500 mg) had been employed. Where the total dosage of thiopentone must be kept to a minimum, as in shock, the maximum use should be made of non-toxic adjuvants both during the induction and maintenance of anaesthesia. Of particular value are nitrous oxide/oxygen mixtures and the muscle relaxants. Large gas flows should be employed immediately after induction to obtain rapid blood saturation. Where carbon dioxide absorption is being used, a maintenance mixture of 2 litres of nitrous oxide and 1 litre of oxygen per minute is satisfactory and full oxygenation is assured (Gray 1954)

Because of the necessity of avoiding hypoxia at all costs in shocked patients, a large bore endotracheal tube should be passed except for very minor procedure. This should be connected directly to the anaesthetic machine and not used just as an airway. The dead space on the face-mask is thus avoided and carbon dioxide accumulation reduced.

Carbon dioxide retention must be prevented during the maintenance of anaesthesia. It causes peripheral vasodilation by both peripheral and central actions and by its central stimulant action on the heart may mask any deterioration in the patient a condition during operation. The fact that a person looks pink when breathing an anaesthetic mixture containing a high percentage of oxygen means only that the arterial blood is saturated with oxygen and does not imply that there is an efficient removal of alveolar

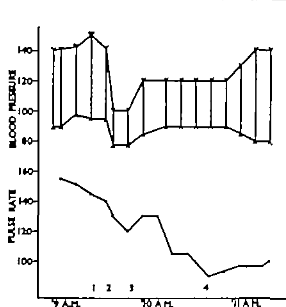
carbon dioxide. Dripps (1947) has described severe post-operative hypotension when patients, who had accumulated carbon dioxide during anaesthesia, were suddenly allowed to breathe atmospheric air. Artifical respiration should be carried out as a routine procedure if a long acting muscle relaxant has been used, where there is detectable respiratory depression following the use of thiopentone, or if a subcutaneous depot of opiate has been released into the blood stream.

Increments of thiopentone if required during the maintenance of anaesthesia, should not exceed 25 mg at any one dose. A constant check must be kept on the blood pressure and pulse readings, and attempts made to correct any variations in these. If it is considered that vasodilation due to thiopentone is playing a part in producing prolonged hypotension a 1 200,000 solution of *l* noradrenaline in 5 per cent. dextrose or normal saline should be given in drip form. One often observes a beneficial effect following the intravenous injection of 0·25 to 0 5 mg digoxin in such circumstances, but this is not a constant finding. It has been suggested by Horton and Davison (1955) that ouabain in doses of 0·25 mg may be of value. Under no circumstances should analeptics with central convulsant properties be used. These increase cerebral oxygen requirements at a time when the circulation may not be able to supply the demand. Furthermore, there is good evidence for the belief that nikethamide has a direct depressant action on the myocardium (Peters and Visscher 1936) (Fig. 18). Vasopressor drugs such as methamphetamine (Methedrine) and adrenaline, part of whose action is to increase cardiac output and the work of the heart, are also better avoided, although phenylephrine (Neosynephrine) and methoxamine (Vasoxyl) may be safe.

Some of the hazards associated with the use of thiopentone in traumatic shock are illustrated in Figures 39 and 40. These patients were United States casualties in the Korean campaign of 1952 (Dripps, 1954).

A completely different approach to the problem of shock and the anaesthetic difficulties encountered in this condition is the so-called "artifical hibernation" popularised by the French workers Laborit and Huguenard (1954). In this, rather than attempting to correct the hypotension the peripheral vasomotor tone is completely abolished by drugs such as chlorpromazine, promethazine, pethidine, procaine or some of the ergot preparations and ' un état physio-biologique stable"

FIG. 39.—A 23 year-old white male (weight 167 lb.) who was pale, "tired and thirsty despite transfusion of 2500 ml. of whole blood. His right leg had been blown off below the knee by a mine.



Anaesthesia: Thiopentone /N_2O/O_2/ether

1. Atropine 1/150 gr. (0·4 mg.) i.v.
2. Thiopentone 200 mg. given slowly over a 10-minute period.
3. Operation commenced.
4. Operation completed.

The relatively high B.P. suggested maximal efforts at compensatory vasoconstriction, and warned of hypotension following the induction of anaesthesia. The hypotension occurred as the thiopentone was administered. A more seriously ill casualty might have had an even greater fall in B.P. Note the reduction in pulse pressure during anaesthesia.

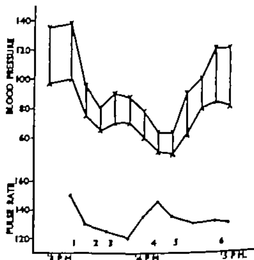
(Dripps, 1954)

FIG. 40.—A 24 year-old white male (weight 160 lb.) with multiple penetrating wounds of the abdomen, lacerations of the liver and right kidney

Anaesthesia: Thiopentone / *d*-tubocurarine chloride/ether

Premedication Atropine 1/150 gr (0·4 mg.) i.m. 2.15 p.m.

1. Thiopentone 375 mg. given over 10 mins.
2. Operation commenced.
3. Ether begun.
4. Three blood transfusions running.
5. Phenylephrine 0·5 mg. i.v.
6. Operation completed.



The pre-anaesthetic pulse rate of 148 and high diastolic pressure should have warned of circulatory instability. Induction of anaesthesia was followed by a sharp decrease in B.P. and a narrowing of the pulse pressure. The addition of ethyl ether vapour at 4 p.m. brought a further reduction in arterial pressure. 5 litres of fluid was administered i.v. during the operation. Phenylephrine appeared to be of value.

(Dripps, 1954)

is produced. It is suggested that overaction of the autonomic nervous system occurs in conditions of shock in an attempt to maintain constant the internal environment and that a partial block of this system diminishes the body's unfavourable reaction to trauma. Sufficient clinical reports have not yet been published to allow a comparison of 'autonomic stabilisation' with orthodox techniques of anaesthesia.

CARDIOVASCULAR DISEASE

This discussion refers to the use of thiopentone in any form of cardiovascular disease in adults, and applies in general to a condition in which there is decreased efficiency of the myocardium or other low output conditions (as in shock). No special mention will be made of the use of the drug for operations on the heart itself, since the same principles apply to its use irrespective of the operative procedure.

The safe administration of thiopentone to persons with cardiovascular disease depends on a proper appreciation of the following

1. Thiopentone is a direct myocardial depressant.
2. The fall in cardiac output is proportional to the concentration of the drug in contact with the heart.
3. The unhealthy myocardium is more susceptible to the effects of thiopentone than the healthy heart muscle.
4. The depressant effects of repeated doses on the myocardium are cumulative.
5. Thiopentone causes peripheral vasodilatation.
6. The arm-brain circulation time is prolonged in some types of heart disease and the onset of sleep may be delayed.
7. Thiopentone causes respiratory depression with resulting hypoxia and carbon dioxide retention.
8. Ventricular arrhythmias, occurring during thiopentone anaesthesia, may be secondary to the accumulation of carbon dioxide.
9. Many of the analeptic drugs and procaine are direct myocardial depressants, and their effects are additive to those of thiopentone.
10. Coughing and straining during anaesthesia result in an increased intrathoracic pressure, with a consequent reduction of venous return to the heart and decreased cardiac output.
11. Laryngeal spasm may cause hypoxia.

Patients who come to operation vary in the severity of their disability (ranging from a minor degree of mitral stenosis to auricular fibrillation with congestive heart failure). Hence they

vary in their sensitivity to the depressant effects of thiopentone some tolerate the drug reasonably well while in conditions such as severe constrictive pericarditis it is contraindicated. Furthermore, as applies in so many other conditions, the skill of the administrator is often of more importance than the actual drugs used. Less harmful results will result from a smooth administration of thiopentone/nitrous oxide/oxygen than from nitrous oxide/oxygen/ether in which there has been coughing or straining even though the direct depressant effect of the latter combination of drugs is less than with the former. This is shown by the many anaesthetic techniques described for the operative relief of mitral stenosis. Some of these, such as that described by Preston (1953), advocate the use of moderate doses of thiopentone, while Gray (1954) produces sleep with nitrous oxide and oxygen, avoiding the stage of excitement by adequate doses of muscle relaxants.

Each patient must be individually assessed as regards the severity of his condition, and the dose of anaesthetic required. The principles to be observed for the safe administration of thiopentone are the same as those advocated for severely shocked patients, and apply irrespective of the actual anaesthetic technique employed. They are briefly summarised as follows

1. Doses should be restricted to a minimum.
2. The drug should be used in a dilute solution.
3. The injection should be given slowly with frequent pauses, to allow the depressant effects to be observed in the presence of slow circulation.
4. Maximum use should be made of non-toxic adjuvants to thiopentone, such as nitrous oxide/oxygen and muscle relaxants.
5. Avoidance of respiratory obstruction, coughing or straining respiratory depression and carbon dioxide retention.

Patients should be adequately premedicated, an opiate or promethazine being the most commonly used drugs. Atropinisation is better avoided in patients with intense tachycardia, although it reduces the likelihood of laryngeal or bronchial spasm. In congestive cardiac failure the pre-operative use of aminophylline may be of value, or this drug may be required during the operation. A means of tracheal suction should always be available, the simplest arrangement being a wide-bore endotracheal tube with a suitable connector such as Cobb's or Magill's T-piece union. Where, because of orthopnoea, it is necessary to induce anaesthesia with the patient sitting up extremely small doses should be

given and the head lowered as soon as the patient becomes unaware of his surroundings In these and in other patients who are cyanosed before operation the effective pre operative administration of oxygen is recommended

It must be remembered that the mean aortic blood pressure is the main factor which governs the coronary blood flow Where there is a history of angina, or where the presence of atheromatous changes in these vessels is suspected, hypotension following the induction of anaesthesia must be treated immediately by adopting a head-down tilt. If this is unsuccessful a noradrenaline drip should be commenced This is preferable to the single injection of the longer acting vasoconstrictors but if a continuous infusion is impracticable, phenylephrine or methoxamine should be given Where induction is carried out in the sitting position these drugs can be incorporated in the thiopentone solution Over transfusion with blood, plasma or plasma substitutes should be avoided at all costs

Care should be taken to ensure that there is no obstruction to expiration when a semi-open circuit is used for the administration of supplementary drugs. With controlled respiration there must be no positive pressure in the rebreathing bag during the passive expiratory phase. Either of these will result in a positive intrathoracic pressure which prevents adequate filling of the heart and reduces the cardiac output. A negative pressure during the expiratory phase is desirable and can be achieved by some mechanical respirators There should always be an adequate pause after expiration

The duties of the anaesthetist in preventing hypoxia in patients with heart disease do not end when the operation is completed. If nitrous oxide has been employed, the sudden cessation of its administration followed by breathing room air may result in a temporary diffusion hypoxia. This can be prevented by the use of oxygen for a few minutes (Fink, 1954) The tendency of patients who have received thiopentone to lapse into a deep sleep when returned to the ward and left undisturbed in bed is a hazard always to be kept in mind when the drug is used. This is of particular importance in subjects with heart disease, since they cannot tolerate even mild degrees of respiratory depression. A close watch should be kept on such cases until they appear to be in full contact with their surroundings, and post-operative sedation

should be withheld until the patients complain of severe pain. One must remember that the stimulant effects of nikethamide on the respiration are very temporary and can give a false sense of security Furthermore, *the use of this drug is not without danger* in the presence of a damaged myocardium which has been depressed by thiopentone. The above remarks concerning respiratory depression on return to the ward apply equally to the reversal of relaxants at the end of the operation.

In children with suspected congenital cardiac abnormalities, the use of rectal thiopentone is frequently recommended for cardioangiography The dose is calculated on a weight basis before the administration, and reduction of this dose will only result in a state of delirium which will have more harmful effects than if a full dose had been used. In contrast to adults, these children tolerate thiopentone well, since the myocardium itself is healthy The only harmful effects are those produced by hypotension (which is rare because of the slow absorption of thiopentone) respiratory depression or respiratory obstruction due to the tongue falling back. During the injection of the dye there is a tendency to laryngeal spasm in light thiopentone anaesthesia. Adequate *atropinisation reduces this tendency* and anaesthesia may be deepened before the injection with supplementary inhalation agents or a further dose of thiopentone given intravenously It is perhaps better to supplement the thiopentone by nitrous oxide/oxygen and give a small dose of suxamethonium prior to injection of the dye. The momentary apnoea is a help during the X ray photography and the effects of this relaxant are *very transitory in the young* *This technique should not* be used by those who are not skilled in endotracheal intubation in children.

RESPIRATORY OBSTRUCTION

Much has been written on the dangers of intravenous anaesthesia in respiratory obstruction, and most workers consider that the use of thiopentone is *contraindicated in* this state. Many fatalities have been reported following hexobarbitone or thiopentone in patients with Ludwig's angina, oedema of the glottis and swellings of the tongue and throat. To explain these fatalities Weese (1939) postulated that the rapid onset of intravenous anaesthesia did not first depress the hypersensitive nerve endings

of the carotid sinus and local trauma or pressure caused impulses to reach the respiratory centre with subsequent cessation of breathing The more gradual onset of inhalation anaesthesia was on the other hand, thought to desensitise these nerve endings by the time the patient was ready for operation.

It is now believed that the problems which are associated with the use of thiopentone in respiratory obstruction are mostly of a purely mechanical nature and are related to the degree of obstruction. In severe cases an adequate respiratory exchange can only be maintained by the help of the accessory muscles of respiration which are under voluntary control When consciousness is lost, their activity is abolished and the intercostal muscles and diaphragm are unable to force sufficient oxygen past the obstruction to maintain an adequate respiratory exchange. In less severe cases, abolition of the use of accessory muscles will result in a degree of hypoxia which can be counteracted for a short period of time by the inhalation of oxygen. Where there is a marked degree of respiratory obstruction the induction of anaesthesia with any agent will lead to trouble unless an adequate airway is first established with a milder degree of embarrassment the use of a volatile or gaseous agent which does not cause severe respiratory depression will be less dangerous than intravenous anaesthesia.

The importance of the accessory muscles of respiration is shown by the following case report in which no respiratory obstruction was present

Male, aged 30 was admitted to hospital with paraplegia due to a suspected tumour of the spinal cord. Morphine gr ¼ (16 mg.) and pentobarbitone 1½ grs. (100 mg) were given prior to a myelogram, and on arrival at the X ray department the patient was found to be very distressed, slightly cyanosed and very dyspnoeic. Since it was impossible to perform a lumbar puncture because of restlessness, 300 mg thiopentone were given. Cyanosis became more marked when consciousness was lost, and though apnoea was only momentary artificial respiration with oxygen was necessary for 5 to 6 minutes and inhalation of oxygen for a further 10 minutes. Fifteen minutes after induction of anaesthesia, although no further anaesthetic had been given and consciousness had returned, the patient was still unable to maintain his colour when breathing air His condition was almost immediately improved following the intravenous injection of 10 mg nalorphine.

In this patient a tumour of the cervical region of the spinal cord abolished intercostal respiration. In the conscious state diaphragmatic activity was sufficient to maintain an adequate respira

tion exchange. After this had been depressed by an opiate barbiturate, the accessory muscles of respiration were requi and even with this aid cyanosis could not be prevented. The of these muscles may have led to the apprehension and dist with a resulting increase in oxygen requirements. When c sciousness was abolished cyanosis resulted because of the los the accessory respiratory muscles and depression of diaphragm activity On return of consciousness the condition reverted what it had been before induction of anaesthesia, and complete covery only followed a reversal of the depressant action of morph

The anaesthetic management of patients with respirat obstruction varies with the severity of the condition. Sedat with opiates or large doses of barbiturates is absolutely con indicated. If the accessory muscles of respiration are requ to draw gases through a narrowed glottis or past any other fo of obstruction, an adequate airway must be established befor depressant drug like thiopentone is given. This can be achie by passing an endotracheal tube under topical analgesia (pref ably through the nose), but where the latter is impossible i necessary to perform a tracheotomy under local analgesia. As alternative a mixture of helium and oxygen may be used, heli having a molecular weight of 4, compared with 28 for nitrog and a mixture of 79 per cent. helium and 21 per cent. oxy (specific gravity 331) can be drawn past an obstruction with l respiratory effort than is required for air (specific gravity 10 The use of this mixture decreases respiratory distress, by help the elimination of carbon dioxide, and it is a valuable agent administer before intubation or tracheotomy If pure helium fed through the nitrous oxide flowmeter the reading must multiplied by 3 3 to get the approximate true rate of flow Volat agents or cyclopropane may be added to the helium/oxyg mixtures provided the concentration of oxygen is not reduced low but care should be taken to avoid respiratory depression w thiopentone, and it is probably better to avoid its use Heli is essential in respiratory obstruction due to tumours of t thyroid gland, since these are usually too low to permit a trac otomy The passage of an armoured endotracheal tube beyo such an obstruction is not always possible. A rubber tube w only be compressed by the tumour resulting in a worsening the position by further reducing the bore of the trachea.

One must not be tempted to depend on dexterity at intubation after thiopentone and a relaxant in patients with Ludwig's angina. Although the muscles are relaxed, visualisation of the glottis may be difficult because of the oedema, and should the first attempts fail, it may be impossible to inflate the patient with oxygen. This is illustrated by an anonymous case report in the *British Journal of Anaesthesia* (1953)

> An African male, aged 18 years, was admitted with a severe Ludwig's angina, but no evidence of any respiratory obstruction. The patient was premedicated with atropine gr 1/100 (0·65 mg) and a sterile tracheotomy set made readily available in the theatre. Thiopentone 400 mg was given followed by 75 mg suxamethonium chloride. On laryngoscopy there was marked oedema of the whole of the pharynx, and the glottis could not be visualised. A tube was passed, but on squeezing the rebreathing bag it became evident that it was in the oesophagus. Further manipulation of the tube precipitated a severe laryngospasm and respiration became completely obstructed. The patient became deeply cyanosed and ceased to make any respiratory efforts. The pulse became almost imperceptible. A tracheotomy was performed and an endotracheal tube inserted through the tracheotomy tube through this the lungs were inflated with oxygen. The patient recovered consciousness in 15 minutes and was discharged from hospital two weeks later none the worse for his ordeal.

In minor degrees of respiratory obstruction, adequate pre oxygenation of the patient may be all that is necessary, but thiopentone must be given in a dilute solution and at such a rate as to minimise respiratory depression. If intubation is contemplated, a small dose of suxamethonium (or preferably suxethonium because of its shorter action) is permissible. All degrees of obstruction are met in clinical practice and each case must be separately assessed. Emphasis is again placed on the fact that the degree of dependence of the patient on the accessory muscles of respiration during consciousness is the most important factor in deciding the anaesthetic technique to be adopted.

Clinical reports of the safe use of thiopentone in patients with respiratory obstruction have all been based on the proper application of the above recommendations Notable among these is the report by Williams and Gruibruck (1943) of 20 administrations of the drug to patients suffering from Ludwig's angina in which no fatalities attributed to thiopentone occurred. The management of such a patient is described below

A woman, aged 42 was suffering from a mild quinsy which was rapidly becoming worse and causing some obstruction to respiration. There was no improvement with intensive chemotherapy and it was considered necessary to relieve the tension as the patient had become very distressed. Oxygen was administered without any improvement and on several occasions trichlorethylene was added to the oxygen in an attempt to produce anaesthesia, but each time it only increased the restlessness.

When seen by an anaesthetist, the patient was extremely apprehensive, severe trismus and slight cyanosis were present, the accessory muscles were being used to their full extent, the pulse was rapid and bounding and the B.P 185/110. Inhalation of 79 per cent. He. and 21 per cent. O_2 immediately improved her condition, the distress became less and the pulse rate slowed. Because of a shortage of supply it was only possible to continue this administration for 10 minutes, but during this time a spray was passed through the nostril and the pharynx and larynx sprayed with 2 per cent. amethocaine and 1 200,000 adrenaline. Two minutes later a nasal endothracheal tube was passed blindly and after a brief period of coughing the patient's condition improved and cyanosis was not present when air was inhaled. Anaesthesia was induced with thiopentone and continued with N_2O/O_2, the patient was put in the head-down position, a sucker placed in the pharynx and a large peri tonsillar abscess incised. The endotracheal tube was left in position until the patient opened her eyes, and on its removal breathing was satisfactory

It is instructive to note that the above procedure was at first considered to be a minor one, the assistance of an anaesthetist not being sought until the patient had been treated for over an hour by the junior hospital staff If advice is sought concerning such a case when respiratory arrest has occurred after the injudicious use of thiopentone, an immediate tracheotomy must be performed. Valuable time will be lost if intubation is attempted, and at present no analeptic is available which will invariably cause an immediate reversal of the narcosis.

The above discussion refers only to patients in whom respiratory obstruction was present before the induction of anaesthesia. Another important group includes the operations during which respiratory obstruction is likely to occur The problem here is the same whatever the anaesthetic used, and where difficulty is likely to arise because of lack of access to the airway an endotracheal tube must be passed before surgery is commenced. The dangers of contamination of the airway by blood, teeth or pus can either be overcome by the use of a light plane of narcosis (and active cough reflex) and posture, or preferably by passing a cuffed

endotracheal tube with the additional safety of a pharyngeal pack. Because of the dangers of laryngeal spasm after stimulation of the larynx during thiopentone narcosis, the first technique is not recommended save for procedures lasting not more than a couple of minutes. The dangers of inhalation of vomitus during induction or during anaesthesia will be discussed in the next section.

ACUTE INTESTINAL OBSTRUCTION

Under this heading vomiting and regurgitation during the induction of anaesthesia with thiopentone will be discussed in detail perhaps a more appropriate sub-title for the first part of this section would be "Thiopentone and the Full Stomach" The importance of this hazard is shown by the report of the Committee of the Association of Anaesthetists of Great Britain and Ireland which considered deaths associated with anaesthesia. Of 232 fatalities attributable in some part to the anaesthesia, regurgitation and vomiting were responsible for 56 (24·2 per cent.) and formed the largest group of cases (*Anaesthesia*, 1952)

In a previous report by two members of this committee, in which were reviewed 43 fatal cases of regurgitation and vomiting the incident occurred during or very soon after induction in 25 patients (58 per cent.), thiopentone was the agent used in 92 per cent. of these, being combined with a relaxant in 48 per cent. (Morton and Wylie, 1951) The high incidence of fatalities reported after thiopentone is partly due to its popularity as an induction agent, but there is good reason to believe that the dangers associated with its use are greater than those which accompany the volatile or gaseous agents.

Morton and Wylie have differentiated between vomiting and regurgitation. The former is an active process initiated by the central action of the anaesthetic, by hypoxia or stimulation (particularly of the oropharynx) during light anaesthesia, and it is rare for thiopentone to initiate vomiting Regurgitation, on the other hand, is considered to be a passive process. With a patient in the horizontal or the head-down position fluid will come out of the stomach as a gravitational effect if the upper and lower ends of the oesophagus are sufficiently relaxed The rapid induction of anaesthesia with thiopentone will provide this relaxation more quickly than the inhalation agents, and provided the prerequisites

are present, regurgitation will occur This is often followed by laryngeal spasm, which may persist until the stimulus is removed. The resulting period of hypoxia may have serious effects on an ill patient. More serious still is regurgitation following a dose of thiopentone which has completely depressed the protective laryngeal reflexes. Even in the absence of active respiration, fluid can flow into the trachea and cause complete respiratory obstruction. Reflex cardiac inhibition may also result from aspiration of stomach contents. Because of their irritant properties, small amounts of aspirated intestinal contents may produce late effects such as bronchopneumonia, atelectasis or lung abscess.

It is of prime importance to appreciate the multitude of circumstances under which *the anaesthetist may encounter a full stomach* before the induction of anaesthesia. Shock has already been referred to in this respect, and mention has been made of the delayed emptying time of the stomach which follows the use of opiates. Morton and Wylie (1951) have classified the circumstances under which material may be present in the oesophagus and stomach as follows

Material in the oesophagus—Oesophageal obstruction or pouch. Pyothorax with oesophageal fistula.
Material introduced into the stomach from above—Food and drink given, i.e. lack of pre-operative preparation. Fluids given for medical reasons, e.g to diabetic patients or stomach washouts not *completely removed. Swallowed blood. Bleeding from nose,* mouth or pharynx due to accident or operation.
Material introduced into stomach from below—Intestinal obstruction. Ileus.
Material from stomach itself—Normal or hypersecretion.
Bleeding from ulcer neoplasm or site of operation.
Prolonged emptying-time of the stomach.

A Pyloric obstruction (including congenital pyloric stenosis).
B Dilatation of the stomach.
C Reflex (1) Emotional states. Pain. Women in labour Shock. Accidents, e.g cuts, fractures, burns.
(2) Peritoneal irritations,[1] e.g perforated ulcer twisted ovarian tumour
D Abdominal distension, e.g large tumours, pregnancy at term, gross ascites.

[1] Appendicitis is not included under this heading as Morton and Wylie believe that vomiting and regurgitation during anaesthesia is not a common occurrence in this condition. They suggest that the explanation may lie in the early vomiting of the disease, followed by a period of anorexia.

E Severe illness. Toxaemia. Moribund patients.
F Drugs Morphine, papaveretum, pethidine, hyoscine, atropine. Most anaesthetic agents.

Several causes are often present together e.g a patient brought to the theatre for resuture of a burst abdomen may be in very poor general condition and may have taken food or fluids just before the incident. There will be shock, emotional disturbance and peritoneal irritation and morphine may have been given.

The variety of clinical conditions is further illustrated by the classification of the 56 cases in the Association of Anaesthetists report, in which nausea and vomiting occurred with fatal results (Table XL)

TABLE XL

Classification of cases in which regurgitation or vomiting occurred with fatal results

(*Anaesthesia*, 1952)

Acute Abdominal Conditions:	
Intestinal obstruction (strangulated hernia, 9)	17
"Second abdominal operations" (*burst abdomen, clot rentation, haemoperitoneum*)	6
Perforated peptic ulcer	4
Twisted ovarian cyst	3
General peritonitis	2
Ascites, gross distension	2
Mesenteric thrombosis	1
Obstetrical Emergencies	4
Non-Abdominal Emergencies (cuts, fractures, burns)	4
Non-Emergency Conditions (inadequate preparation)	5
Diabetic Patients (glucose solution given by mouth)	4
Various (partial gastrectomy 2 gastro-enterostomy 1; broncho-oesophageal fistula, 1)	4
	56

In many patients, such as those suffering from intestinal obstruction or having a history of a recent meal one can be certain that there is fluid or food in the stomach, and the necessary precautions taken. It is in the doubtful cases where accidents are likely to happen and where the anaesthetist may be caught unprepared. Unless a 'normal patient has been prepared for an elective operation in the usual way, one must suspect the presence of a full stomach.

The advice *par excellence* is to pass a large-bore stomach tube

before induction of anaesthesia in all patients where there is any suspicion that the stomach is not empty However the stomach may rapidly fill again. More likely an attempt will have already been made to empty it through a Ryle's tube before the patient comes to the anaesthetic room. A Ryle's tube can give a false sense of security since it is easily blocked and will not allow passage of solids. Morton and Wylie suggest that it has only two uses from the anaesthetist's point of view to obtain information about the stomach contents, e.g whether normal or faeculent, and to remove fluid from the stomach immediately before induction. The author (1950) has compared the pre-operative use of a stomach tube and Ryle's tube in 62 cases of intestinal obstruction. With the latter regurgitation occurred at some stage of the operation in 15 out of 42 patients, while the only trouble encountered in 20 cases in which a stomach tube was used was in one patient in whom this was inadvertently removed during laryngoscopy The size 12 (7 mm. diameter) oesophageal tube has been recommended as an alternative to the full-size stomach tube (13 mm. diameter) and can usually be passed through the nose. It will allow solids to pass and large amounts of fluids can be aspirated, but if left *in situ* during induction, when the sphincters are released, fluids may escape around the tube. This latter is less likely to happen with the full-size stomach tube.

The passage of a stomach tube can be a distressing procedure, and may upset a seriously ill patient. Reference has already been made to the synchronous passage of this tube and the injection of a small dose of thiopentone to make the patient less aware of the proceedings. A test dose of relaxant should be given first if a long acting relaxant is to be used during the operation. This facilitates passage of the stomach tube. Before the above manœuvre is carried out, the patient should be encourgaed to breathe oxygen for 5 to 10 minutes Once the stomach has been emptied, a further small dose of thiopentone should be given if required, followed by a full dose of relaxant and intubation. Suxamethonium may be preferred for intubation, which should be with a cuffed tube and a direct connection made to the anaesthetic apparatus. It is not sufficient to use the endotracheal tube as an airway and strap on a face-mask. Pharyngeal suction is essential during removal of the stomach tube as it often leaves a pool of fluid behind it.

If it is desired to use thiopentone and a full dose of relaxant without a stomach tube, a 20-degree foot-down tilt should be adopted (Morton and Wylie, 1951) The hypotensive effects of thiopentone are accentuated by this posture and the injection must be given slowly and dosage kept to a minimum. The intravenous injection of 5 to 10 mg methoxamine a minute or two before the thiopentone may be of value in seriously ill patients.

Morton and Wylie consider that technique involving thiopentone and a relaxant are unsuitable for beginners. They recommend the nitrous oxide/oxygen/ether sequence, giving carbon dioxide if required to facilitate the introduction of ether The safety claimed for this technique depends on maintaining an active cough reflex and the ability to clear material from the mouth and pharynx before the next breath is taken. Be this as it may thiopentone should not be administered either by beginners or experienced anaesthetists, to patients with a full stomach unless precautions are taken to avoid the aspiration of regurgitated gastro-intestinal contents. The exact method of prevention is not of great importance, and each anaesthetist should use the technique with which he is best acquainted. Of greater importance is an appreciation of the circumstances under which regurgitation may be encountered and an understanding of the dangers involved.

While the aspiration of intestinal contents is the greatest hazard encountered in patients with acute intestinal obstruction, it is not the only problem associated with this condition. If vomiting has occurred, or if a large volume of fluid has been aspirated from the stomach, there will be some degree of dehydration which should be partly corrected if possible. Gastric contents contain approximately 60 mEq sodium, 90 mEq chloride and 10 mEq potassium per litre, so that in pyloric obstruction there will be an increased chloride loss in relation to sodium a relative increase in plasma base and consequent alkalosis Small intestinal secretions contain more sodium than chloride, so that in small bowel obstruction more bicarbonate than chloride is lost and acidosis may result.

The fluid of preference for emergency treatment of electrolyte balance due to vomiting is normal saline, but in patients who have lost small bowel juices this should be combined with M/6 sodium lactate. Merivale (1953) and others have given formulae from which can be estimated the amount of sodium and chloride to be administered, depending on the plasma sodium and chloride

levels The latter are not usually available in the short time before operation. In their absence, over infusion with electrolytes is inadvisable, especially in view of the sodium and chloride retention and increased output of potassium which follow all surgical operations.

Blood or a plasma substitute may be required to correct anaemia or protein deficiency and make the patient fit for operation, even though there has been no blood loss. This applies particularly to elderly debilitated patients and in cases of long standing obstruction where no food may have been taken for several days. Where post-operative hypotension will not respond to transfusion or where impending heart failure is present, 0·25 mg strophanthin G (ouabain) or 0 5 mg digoxin should be given intravenously

Although the above details are not directly connected with the administration of thiopentone, they help to make the patient less sensitive to the depressant effects of the drug Another point worth mentioning is to induce anaesthesia on the operating table. This cuts down the duration of the anaesthesia and eliminates changes in posture under anaesthesia which elderly patients tolerate badly

URAEMIA

Reference has already been made to the sensitivity to thiopentone induced by a raised blood urea. However in uraemia this rise in blood urea is only one of many electrolyte derangements and is accompanied by a rise in blood chlorides with a fall in carbon dioxide combining power The upset may be so great as to result in loss of consciousness, which always occurs in the terminal stages of the condition. Irrespective of the cause, uraemia results in an even more marked sensitivity to thiopentone than that which occurs in the presence of a raised blood urea level due to ingestion of urea.

In Fig 41 are shown details of several administrations of varying doses of thiopentone to one patient with blood-urea levels varying between 20 and 90 mg (due to prostatic enlargement) The duration of narcosis is taken as the time between the injection of thiopentone and movement of the patient in response to a constant stimulus (passage of a cystoscope). This case report illustrates the above statements regarding sensitivity to thiopentone and shows that changes in the blood-urea level, which are not considered to be of great clinical importance, may markedly affect the duration of anaesthesia.

Results with experimentally induced uraemia in dogs, produced by vesico-appendicular anastomosis and division of the urethra show that, with a raised blood urea, the total duration of thiopentone narcosis is increased out of proportion to the increase in

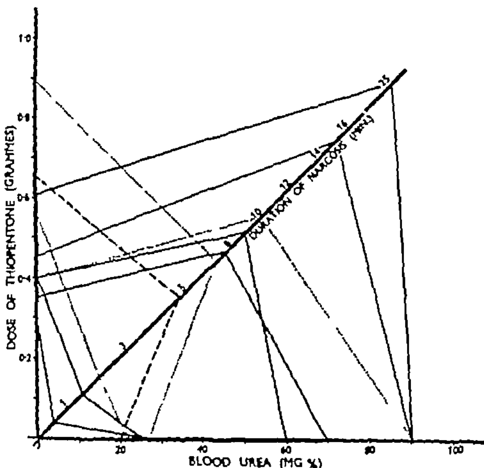


FIG. 41.—Duration of anaesthesia with varying doses of thiopentone in response to a constant stimulus at different blood urea levels in one patient.

the duration of surgical anaesthesia (Dundee and Annis, 1955) This is of great clinical importance, since the use of moderate doses of thiopentone as the sole narcotic for minor procedures such as cystoscopy may in the presence of a raised blood urea result in very prolonged post-operative sleep In the patient referred to in Fig. 41 the total sleeping time after 600 mg thiopentone when the blood urea level was 90 mg per cent. exceeded 12 hours, while when the blood urea was only 25 per cent. consciousness was regained within one hour after 900 mg of thiopentone.

Because of this post-operative somnolence, thiopentone sl not be used as the sole narcotic even for minor procedures the blood urea is raised. Small doses, sufficient to induce s are permissible, but with very high blood-urea levels even are better omitted. Where there is already some cloudin consciousness due to uraemia, the use of thiopentone is co indicated. In the absence of this symptom it is difficult t dogmatic and state a level of blood urea above which one sh not use the drug The following case-reports may throw s light on this subject

Twenty-three hours sleep followed the use of 400 mg thiopen to a 133-lb (60-kg) man with a blood urea of 148 mg per cent.

A fatal outcome resulted from the administration of 400 mg. t pentone to a 126-lb (57 kg) man with a blood urea of 208 mg. cent. death occurring 21 hours after the administration, due to p longed depression.

To control convulsions, thought to be due to uraemia, 100 thiopentone were given. This produced unconsciousness wh terminated fatally after 38 hours. The blood urea was 400 mg per c 12 hours after the administration of the thiopentone.

It is in patients who come to operation for prostatecton especially if the obstruction has been long standing, that a rai blood urea is most commonly encountered in clinical practi Subarachnoid or epidural block is widely used for this operatio especially where bleeding points in the prostatic bed are di thermised under direct vision. It is not proposed to discuss th control of blood pressure during these operations. Provided th area of analgesia is sufficient for the operative procedure, the us of small amounts of thiopentone to produce light narcosis at th beginning of the operation is reasonably safe. However toward the end of the operation the patient may begin to react, presumabl due to stimuli from such sources as prolonged pressure by shoulder rests or even from pressures by the surgeon or assistant on the chest, and it may be tempting to give more thiopentone This is to be avoided, and use should be made of nitrous oxide, oxygen and if necessary trichlorethylene alternatively a small dose of pethidine or levorphan can be given intravenously It is obvious that care should be taken to avoid any stimulation of non-analgesic areas, as more thiopentone will be required to obtund the effects of this stimulation and maintain sleep These include the application of towel-clips, insertion of nasal catheters

(for the administration of oxygen) too far into the nostril or too tight application of a face mask. A less obvious source of stimulation is that due to too frequent inflation of the sphygmomanometer cuff for blood pressure estimations

Thiopentone should never be used alone to 'cover' an inadequate spinal analgesic if there is any elevation of the blood urea The doses required under these circumstances are similar to those required when it is used as the sole narcotic, and a very great delay in the return of consciousness may ensue.

Apart from the prolonged coma which may result from the use of thiopentone, it must be remembered that uraemic patients are usually elderly and often have other complicating medical conditions. The precautions advised above for the administration of thiopentone to subjects with cardiovascular disease should be strictly adhered to. In emergency operations patients may be severely dehydrated, either due to their unwillingness to drink because of urinary retention or due to vomiting or, they may have a full stomach. Where possible the fluid and electrolyte balance should be restored before induction of anaesthesia as an increase in the circulating blood volume will reduce the cardiovascular toxicity of thiopentone. Where the presence of a full stomach is suspected, the case should be treated appropriately

LIVER DAMAGE

The importance of the liver in the detoxication of thiopentone has already been discussed, and mention has been made of the paucity of case reports of prolonged narcosis following the use of the drug in hepatic dysfunction. The reasons for this will again be mentioned.

(a) Recovery from small doses of thiopentone is due to distribution to non-nervous tissues and is independent of detoxication Large doses of the drug *must be given before* any prolongation of narcosis occurs in patients with liver damage.

(b) There is a great reserve of liver tissue, and degrees of liver disease are necessary before there is pairment of detoxication.

To emphasise the possibility of delayed recovery f doses of thiopentone in patients with hepatic dysf following two case reports are included. These are

Because of this post-operative somnolence, thiopentone should not be used as the sole narcotic even for minor procedures when the blood urea is raised. Small doses, sufficient to induce sleep are permissible, but with very high blood urea levels even these are better omitted. Where there is already some clouding of consciousness due to uraemia, the use of thiopentone is contra indicated. In the absence of this symptom it is difficult to be dogmatic and state a level of blood urea above which one should not use the drug The following case-reports may throw some light on this subject

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LIVER DAMAGE

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(*a*) Recovery from small doses of thiopentone is due to distribution to non nervous tissues and is independent of detoxication. Large doses of the drug must be given before any prolongation of narcosis occurs in patients with liver damage.

(*b*) There is a great reserve of liver tissue, and very severe degrees of liver disease are necessary before there is much impairment of detoxication.

To emphasise the possibility of delayed recovery from large doses of thiopentone in patients with hepatic dysfunction, the following two case-reports are included. These are selected from

publications from countries as far apart as Britain (Dundee, 1952a) and Pakistan (Taraporevela and Khan, 1950)

Male aged 32, weight 147 lb (67 kg). Admitted to hospital with compound fractures of tibia and fibula. Surgical toilet was carried out under thiopentone/nitrous oxide/oxygen/ether anaesthesia. The exact amount of thiopentone given was not known, but thought to be in the region of 1 g. Anaesthesia was uneventful with no delay in recovery

Five days later the fracture required remanipulation. The patient felt ill, temperature was 102 F., pulse 90/minute. He was shivering and complaining of pain in both loins. 400 mg thiopentone were given quickly to produce relaxation, followed by 300 mg three minutes later At the end of the operation he was deeply unconscious and a pharyngeal airway was inserted. He showed no reaction to supraorbital pressure 3 hours after his operation and did not cough out the airway for a further 2 hours. Consciousness was not regained until 18 to 19 hours after the thiopentone administration.

Jaundice appeared on the day following operation, was subsequently shown to be due to Weil's disease, the leptospira icterohaemorrhagica being recovered from the urine.

An army drum major aged 22 was operated on for a minor complaint. Routine pre-anaesthetic examination revealed no abnormality Morphine gr $\frac{1}{4}$ (16 mg) was given one hour before operation. One g of 5 per cent. thiopentone was administered intravenously there being no untoward behaviour during the course of the injection and the whole anaesthetic went smoothly Nothing abnormal was observed in his condition after operation, save that consciousness did not return and reflexes remained absent until death occurred 7 hours after the anaesthetic.

Autopsy The liver was enlarged and congested and the cut surface was smooth and purple. On histological examination it showed advanced fatty degeneration verging on necrosis, most of the parenchymatous cells showing fat vacuoles of varying size. The larynx, trachea and bronchi were full of froth and slightly congested Both lungs seemed dark and heavy and frothy fluid exuded on pressure from the cut surfaces. Microscopic examination revealed dilatation of the capillaries, *the alveoli were full of amorphous granular material* indicative of serous fluid and a few 'heart failure' cells were seen. The left coronary artery was narrow and sclerosed in the middle part and slight atheromatous changes of the aorta were seen. The heart showed an increase in interstitial fibrous tissues and some fatty degeneration of muscle fibres.

In the former patient the depth of unconsciousness at the end of the operation was probably less than in the second, as judged by extrusion of the airway after 5 hours. This may have been due to the smaller dose of thiopentone administered. However

the fatal outcome in the second case, as compared with the first, may also be related to the general condition of the two patients, the second may have been less able to stand a period of deep coma and slight hypoxia. This applies to most patients with liver disease, especially where cirrhosis is present, since this is frequently accompanied by ascites, which may interfere with respiration. In alcoholic cirrhosis the accompanying malnutrition may have affected the myocardium, which will be less able to withstand hypoxia.

If prolonged coma follows the injudicious use of thiopentone, the treatment should be as for any case of barbiturate poisoning. Correction of hypoxia is the underlying principle. An endotracheal tube should be passed if the cough reflex is absent and oxygen administered respiration being controlled where there is any reduction in the tidal volume. The administration of oxygen by an open or semi-open circuit may unduly dry the tracheal mucous membrane and the gas should be suitably humidified. Tracheal secretions must be aspirated at frequent intervals and the patient's posture changed hourly A close watch must be kept for the development of areas of atelectasis. These can usually be relieved by percussion of the chest wall, but if this fails, bronchoscopy should be carried out. Tracheotomy should be considered when it is found difficult to remove secretions in the endotracheal tube and when repeated areas of atelectasis are occurring Intensive chemotherapy is essential. Blood pressure, pulse rate and rectal temperature should be charted at regular intervals and the presence of cardiac irregularities taken as an indication of the accumulation of carbon dioxide. It will be recalled (Fig 22) that blood pressure rises are not observed in the presence of deep barbiturate narcosis. Hypotension should be corrected where possible, but the dangers of over transfusion must be remembered and pulmonary oedema avoided at all costs.

The effectiveness of the above treatment depends on the thoroughness with which it is carried out. Proper planning is essential and a scheme must be worked out for each individual patient. A chart is placed above the bed showing the time each observation or treatment is due. One person must be made responsible for this treatment, and if it is ascribed to junior medical or nursing staff instruction should be given as to what

danger signs to look for and the emergency treatment for any crisis. All apparatus likely to be needed should be close at hand and tested spare cylinders of oxygen should be readily available of equal importance, is that the person in charge should know where to obtain assistance or advice without delay

Much has been written on the use of analeptic drugs in the treatment of barbiturate poisoning Nikethamide, picrotoxin, leptazol, strychnine, amphetamine, sodium succinate, lobeline, theophylline and multiple vitamins have been tried. Nilsson (1950) considers that the treatment should be as for deep anaesthesia (outlined above) with no analeptics. Koppanyi and Fazekas (1952) have criticised this 'pharmacotherapeutic nihilism' and consider that leptazol and picrotoxin are most valuable weapons in the treatment of barbiturate poisoning These drugs do not increase the rate of breakdown of thiopentone but raise the blood barbiturate level at which consciousness returns. They are convulsant in large doses, and increase cerebral oxygen consumption, their action is only transient and no analeptic drug should be given in deep thiopentone narcosis. When the laryngeal reflexes have returned and the depth of the coma is less, an injection of 5 to 20 ml. Megimide (p 267) may be of value. This often produces a return of consciousness and once the patient has regained contact with the environment a relapse is uncommon, especially if sufficient stimulation, such as someone talking to him, is maintained and the patient not left undisturbed in bed.

An increased duration of narcosis is not the only reason why thiopentone should be sparingly administered to patients with liver damage. In Fig 25 it is shown that large doses of thiopentone can cause temporary impairment of the hepatic function and it seems unwise to administer more than the minimum possible dose of a hepatotoxin to a patient with an already damaged liver The effects overdosage in one such case will be described later

The response to muscle relaxants is also altered in patients with liver damage. The lowered plasma cholinesterase which accompanies this condition leads to sensitivity to suxamethonium. This is a well known clinical entity and many cases have been reported in the literature. Less well known is the resistance to those relaxants which act by competition block (Dundee and Gray 1951 1953) Thus, sensitivity to thiopentone and resistance to

relaxants may be observed at the same time in patients with liver dysfunction This is illustrated by the following case-report, in which the patient also showed early resistance to both thiopentone and *d* tubocurarine chloride associated with acquired tolerance to sedative and analgesic drugs.

A man, aged 20, had a long series of operations.

August 28th 1949—Gangrenous appendix removed

January 9th, 1950—Ileo-ascending colostomy for subacute intestinal obstruction.

June 6th—Abscess in loin incised under thiopentone (400 mg) and cyclopropane anaesthesia.

September 10th—Readmitted to hospital with severe pain in lumbar region and hypogastrium. Large doses of sedative and analgesic drugs were being administered.

October 10th—Hb 85 per cent., weight 136 lb. (57 kg)

October 11th—Laparotomy and drainage of numerous intra abdominal abscesses. Premedications morphine gr $\frac{1}{6}$ (10 mg) and atropine gr $\frac{1}{100}$ (0·65 mg). Anaesthetic *d* tubocurarine chloride/thiopentone/nitrous oxide/oxygen/ether (closed circuit) The patient was very resistant to all these agents, *d* tubocurarine chloride 80 mg., thiopentone 2 5 g. and ether 56 ml. were required during the operation, which lasted 135 minutes. In spite of these large doses, respiration was never very depressed and no neostigmine was required at the end. Slight jaundice appeared 12 hours after operation and lasted for 24 hours. Urinary urobilinogen was present to a dilution of 1 in 60, the serum bilirubin level was 1·0 mg per 100 ml., cephalin cholesterol +++ but other liver function tests were normal. Pus from the abscesses contained actinomyces.

January 9th, 1951—Hb 58 per cent. general condition poor Doses of drugs required to alleviate pain had greatly increased. Excess urobilinogen had disappeared from the urine and the serum-bilitulbin level was normal.

January 16th—Evacuation of pus from the loin. Premedication as on 11 10.1950. Anaesthetic *d*-tubocurarine chloride/thiopentone/cyclorpropane/ether The patient s resistance to anaesthetic drugs was maintained, *d*-tubocurarine chloride 20 mg and thiopentone 1 g being required for endotracheal intubation, which was followed by violent coughing and very little respiratory depression. Large amount of cyclopropane and ether were required.

February 5th—The patient had deteriorated and was emaciated, weighing 112 lb. (51 kg). A sinus was explored down to the lumbar spine under thiopentone (500 mg) and cyclopropane anaesthesia. Very little cyclopropane was required.

February 13th—The wound was packed under thiopentone (250 mg) and cyclopropane anaesthesia. Again very little cyclopropane was required.

danger signs to look for and the emergency treatment for any crisis. All apparatus likely to be needed should be close at hand and tested spare cylinders of oxygen should be readily available of equal importance, is that the person in charge should know where to obtain assistance or advice without delay

Much has been written on the use of analeptic drugs in the treatment of barbiturate poisoning Nikethamide, picrotoxin, leptazol, strychnine, amphetamine, sodium succinate, lobeline, theophylline and multiple vitamins have been tried. Nilsson (1950) considers that the treatment should be as for deep anaesthesia (outlined above) with no analeptics Koppanyi and Fazekas (1952) have criticised this pharmacotherapeutic nihilism and consider that leptazol and picrotoxin are most valuable weapons in the treatment of barbiturate poisoning These drugs do not increase the rate of breakdown of thiopentone but raise the blood-barbiturate level at which consciousness returns. They are convulsant in large doses and increase cerebral oxygen consumption, their action is only transient and no analeptic drug should be given in deep thiopentone narcosis. When the laryngeal reflexes have returned and the depth of the coma is less, an injection of 5 to 20 ml. Megimide (p 267) may be of value. This often produces a return of consciousness, and once the patient has regained contact with the environment a relapse is uncommon, especially if sufficient stimulation, such as someone talking to him, is maintained and the patient not left undisturbed in bed.

An increased duration of narcosis is not the only reason why thiopentone should be sparingly administered to patients with liver damage. In Fig 25 it is shown that large doses of thiopentone can cause temporary impairment of the hepatic function and it seems unwise to administer more than the minimum possible dose of a hepatotoxin to a patient with an already damaged liver The effects overdosage in one such case will be described later

The response to muscle relaxants is also altered in patients with liver damage. The lowered plasma cholinesterase which accompanies this condition leads to sensitivity to suxamethonium. This is a well-known clinical entity and many cases have been reported in the literature. Less well known is the resistance to those relaxants which act by competition block (Dundee and Gray 1951 1953) Thus, sensitivity to thiopentone and resistance to

relaxants may be observed at the same time in patients with liver dysfunction. This is illustrated by the following case report, in which the patient also showed early resistance to both thiopentone and *d* tubocurarine chloride associated with acquired tolerance to sedative and analgesic drugs

A man, aged 20 had a long series of operations.

August 28th, 1949—Gangrenous appendix removed.

January 9th 1950—Ileo-ascending colostomy for subacute intestinal obstruction.

June 6th—Abscess in loin incised under thiopentone (400 mg) and cyclopropane anaesthesia.

September 10th—Readmitted to hospital with severe pain in lumbar region and hypogastrium. Large doses of sedative and analgesic drugs were being administered.

October 10th—Hb 85 per cent., weight 136 lb (57 kg).

October 11th—Laparotomy and drainage of numerous intra abdominal abscesses. Premedications morphine gr $\frac{1}{6}$ (10 mg) and atropine gr $\frac{1}{100}$ (0·65 mg). Anaesthetic *d* tubocurarine chloride/thiopentone/ nitrous oxide/oxygen/ether (closed circuit). The patient was very resistant to all these agents, *d* tubocurarine chloride 80 mg., thiopentone 2 5 g and ether 56 ml. were required during the operation, which lasted 135 minutes. In spite of these large doses, respiration was never very depressed and no neostigmine was required at the end. Slight jaundice appeared 12 hours after operation and lasted for 24 hours. Urinary urobilinogen was present to a dilution of 1 in 60, the serum biliruban level was 1·0 mg per 100 ml., cephalin cholesterol +++ but other liver function tests were normal. Pus from the abscesses contained actinomyces.

January 9th, 1951—Hb 58 per cent., general condition poor Doses of drugs required to alleviate pain had greatly increased. Excess urobilinogen had disappeared from the urine and the serum bilituibin level was normal.

January 16th—Evacuation of pus from the loin. Premedication as on 11 10.1950 Anaesthetic *d* tubocurarine chloride/thiopentone/ cyclorpropane/ether The patient s resistance to anaesthetic drugs was maintained, *d* tubocurarine chloride 20 mg and thiopentone 1 g being required for endotracheal intubation, which was followed by violent coughing and very little respiratory depression. Large amount of cyclopropane and ether were required.

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February 13th—The wound was packed under thiopentone (250 mg) and cyclopropane anaesthesia. Again very little cyclopropane was required.

or a similar drug is recommended, provided the dose is adjusted to the condition of the patient and respiratory depression is avoided. Endotracheal intubation is essential for most neurosurgical operations and, subject to the above requisites, each anaesthetist should use a technique with which he is familiar. The author has found the following to be reliable and without deleterious effects of intracranial pressure.

Premedication varies, but all adults receive $\frac{1}{100}$ gr (0·65 mg.) atropine, and no opiate is given. Where mild sedation is required, 25 to 50 mg promethazine is combined with the atropine. If there is any doubt about the timing of the hypodermic injection of atropine, a further dose is given intravenously.

Induction is with a slow injection of sufficient thiopentone to abolish the corneal reflex. This is followed by 25 to 40 mg suxamethonium, the lungs being inflated 3 to 4 times with nitrous oxide/oxygen/trichlorethylene after apnoea has occurred. The pharynx, larynx and trachea as far as the carina are thoroughly sprayed with 4 per cent. lignocaine. If spontaneous respiration has returned, anaesthesia is continued with nitrous oxide/oxygen/trichlorethylene for a further 2 minutes, a *supplementary dose of thiopentone being injected if the* corneal reflex has returned. In the absence of spontaneous respiration the lungs are rhythmically inflated with the above mixture for 2 minutes. If necessary 25 mg suxamethonium are given before the oral intubation, which is preferably carried out on an apnoeic patient so as to avoid the possibility of coughing. A smooth return of spontaneous respiration can be achieved by inflation with nitrous oxide/oxygen/ether after intubation. Ether is discontinued once a satisfactory excursion has returned, anaesthesia being continued with 9 litres nitrous oxide and 3 litres oxygen per minute using an open T piece technique with or without trichlorethylene. The use of pethidine is not recommended *in the presence of a raised intracranial pressure*, save in doses of 15 to 20 mg where trichlorethylene has raised the respiratory rate above 28 per minute. Levorphan in doses of 0·4 mg is often a useful adjuvant to nitrous oxide and produces no detectable respiratory depression.

ASTHMA

Opinions differ as to the advisability of using thiopentone in asthmatic patients. As with every other pathological state, each case must be assessed individually and no hard and fast rules can be given. Thiopentone does not markedly depress laryngeal reflexes. It causes slight constriction of the lumen of the bronchial tree, and if a predisposing cause is present, bronchospasm is more likely to follow *its administration than if a bronchodilator such as*

di-ethyl ether had been used. During very deep anaesthesia the bronchi are relaxed by all anaesthetic agents, but it must be remembered that chronic asthmatics have often an unhealthy cardiovascular system.

The most important step is to try to relieve the bronchospasm before the administration of the thiopentone. This can often be achieved by using a bronchial dilator drug such as ephedrine, isoprenaline or aminophylline, followed by encouraging the patient to cough, or instituting postural drainage for the removal of secretions. Despite the theoretical disadvantage of making the secretions more tenacious, a full dose of atropine or hyoscine should be given. Morphine is better avoided since it causes bronchoconstriction and if sedation is required, pethidine is preferred with or without promethazine.

When a patient in status asthmaticus is presented for operation if this condition cannot be relieved by ephedrine, adrenaline, *isoprenaline or aminophylline, thiopentone should not be given* and local or spinal analgesia is preferred. Where a mild degree of spasm still persists in spite of treatment, oxygen inhalation should be instituted and 20 mg pethidine given intravenously Aminophylline should always be at hand for immediate intra venous *administration if necessary Before administration of* thiopentone, 5 per cent. carbon dioxide should be added to the oxygen and the rate of injection should be sufficiently slow as not to abolish the stimulant effect of the carbon dioxide. Nitrous oxide is started as soon as consciousness is lost (still continuing *the carbon dioxide) and methyl n propyl ether or divinyl ether* added gradually The latter drugs seem to be as effective as diethyl ether in relieving bronchospasm and have the advantage of being less irritant, thus allowing a more rapid increase in concentration. Where anaesthesia is expected to be prolonged, an early change *should be made to* diethyl ether or trichlorethylene if necessary with further intravenous pethidine Where muscular relaxation is required suxamethonium or gallamine triethiodide are preferred to *d* tubocurarine chloride, and care should be taken in the use of neostigmine at the end of the operation

In patients who are known *asthmatics, but not suffering from* the disease at the time of operation, no trouble need be expected from the use of thiopentone Premedication should be as sug gested above, and the use of pethidine immediately before induc-

tion and carbon dioxide for a few minutes after the loss of consciousness is recommended.

PORPHYRIA

The harmful effects of barbiturates, especially thiopentone, in porphyria, have been noted by several writers. Dundee and Riding (1955) reviewing the cases reported in two journals between 1948 and 1953 found details of 37 attacks of acute porphyria occurring in 32 patients. There were 15 operations in this series, thiopentone being administered for 13 of these. Paralysis occurred in all patients who received thiopentone and proved fatal in 5 instances. In the light of our present knowledge, porphyria must be considered an absolute contraindication to the use of any barbiturates. The disease is very uncommon and can take so many clinical forms that a brief description of it will be given, with particular reference to how the anaesthetist may encounter it in practice and the clinical features that may aid its recognition.

The exact aetiology of porphyria is unknown it is a disease of metabolism involving pyrolle pigments which take part in cell respiration. Many classifications have been suggested, and the following seems to meet with most approval

Congenital.
Porphyria cutanea tarda.
Acute intermittent porphyria.

This division is by no means clear-cut, and overlapping occurs.

The congenital type is characterised by photosensitivity pigmentation *of bones and teeth, and is familial. The cutaneous variety* shows photosensitivity and recurrent skin lesions often of a blistering type, due to heat or minor trauma. Here again there is evidence of a familial background.

Acute attacks may occur without any known precipitating factors, or in known porphyrics. In the latter several drugs as well as barbiturates seem to evoke an attack. These include sulphonamides, sulphonal and possibly alcohol. The clinical picture of acute attacks has been described as resembling lead poisoning in several respects. It may be ushered in by abdominal pain, distension, nausea and vomiting followed by the passage of reddish-coloured urine. It is at this stage that an exploratory laparatomy may be carried out. Weakness follows within a few days of the onset of the attack, followed by a lower motor neurone paralysis. This may stimulate paralysis of the Landry type or that seen in familial periodic paralysis of neuromyelitis. Death may occur from respiratory paralysis or recovery take place in 6 to 32 weeks.

The importance of recognising porphyria is illustrated by the following cases reported by Dean (1953)

A woman aged 29 with no relevant history became paralysed 3 days following a uterine curettage under thiopentone anaesthesia. Recovery took 7 months. Two years later after a dental extraction for which thiopentone was administered paralysis again occurred recovery taking 5 months.

After hysterectomy for which a barbiturate was administered the patient was unable to walk for 6 months Nineteen years later she received thiopentone, and the resulting paralysis proved fatal in 6 weeks. Dean found a family history of skin sensitivity in this patient, who had previously been regarded as a neurotic.

A girl of 19, having had several attacks of paralysis following oral barbiturates, had thiopentone for an exploratory laparotomy Within 3 days complete paralysis had occurred, and this proved fatal 5 days later

A family history of five relatives who died from general paralysis after drugs and anaesthetics was present in a woman who herself suffered from skin blisters. After two operations at which thiopentone was administered, she suffered from paralysis and delirium, but eventually recovered

It can be seen that the anaesthetist may encounter porphyria at any stage of the disease. In the latent phase there are some guides to its detection such as a history of paralysis from a previous operation or after taking sedatives. The skin changes of the cutaneous variety may be obvious as scars from previous blisters of the hands, or the patient may volunteer the history of a sensitive skin. There may be a history of relatives having died after anaesthetics, and while this may have no relationship to porphyria, at least it should arouse suspicion, and lead to a more detailed questioning of the patient. Of most positive value would be a history of passing red urine, but except in the case of an elective operation such information is unlikely to be volunteered by patients as they would see no relationship between this and their present complaint.

The most difficult case to detect is the "acute abdomen of unknown aetiology That there is no previous history of porphyria is apparent from the fact that a laparotomy is contemplated and the stage of porphyrinuria may not have been reached. Whereas in the case of an elective operation it seems clear that thiopentone can precipitate an attack of acute porphyria with resulting paralysis, in the emergency operations the acute attack

has already started and the chances of a patient having paralysis are already great, whether thiopentone be given or not. There seems little justification in withholding thiopentone from every patient having an emergency laparotomy in whom the exact diagnosis has not been made, in the remote chance that the abdominal pain may be due to acute porphyria.

Porphyria is a rare disease in Britain, being more prevalent in the Scandinavian countries and South Africa. In these countries particular attention should be paid to the above remarks. In view of the dire effects of the use of thiopentone in elective operations in known porphyrics, all such patients should be given a letter drawing attention to their disease, to be handed to the surgeon or anaesthetist before any operation is contemplated. By this arrangement fatalities similar to those mentioned above can be avoided.

There is little information available as to the safest anaesthesia to use in porphyric patients. Dean (1953) states that ether can be given with safety It would seem wise to use agents which are excreted unchanged and which do not require any metabolic processes for recovery from anaesthesia. These include nitrous oxide/oxygen, ether and paraldehyde.

DYSTROPHIA MYOTONIA

This rare disease is unique in that abnormal depression of respiration has been reported after the administration of small doses of thiopentone. Data on this subject is limited to three cases reported by the author (Dundee, 1952b) In the first patient, 10 minutes apnoea and 30 minutes respiratory depression followed 500 mg thiopentone, and 40 minutes respiratory depression was produced by 250 mg thiopentone in the second case. A reduction of 48 per cent. in the minute volume was produced by 50 mg thiopentone in the third case, compared with a 30 per cent. increase from this dose in normal subjects. The duration of narcosis appears to be normal in patients with dystrophia myotonia. The failure of carbon dioxide to stimulate respiration (although it causes a rise in blood pressure) and a very transient stimulation by nikethamide, suggests that the overaction of thiopentone is peripheral rather than central in origin and is possibly an action on abnormally sensitive muscles

Until further clinical reports are forthcoming it is advisable that doses of thiopentone administered to such patients should not exceed 100 mg Where a larger dose has been inadvertently given and where severe respiratory depression has occurred, it should be remembered that consciousness may return before the patient can maintain an adequate respiratory exchange. It is essential that artificial respiration be carried out with a mixture of nitrous oxide and oxygen rather than with oxygen alone. The use of carbon dioxide or other respiratory stimulants is not recommended.

Such is the rarity of dystrophia myotonia and of its sufferers coming to operation that it is not considered necessary to give a detailed description of the disease or how it may be detected. It is sufficient to quote the definition given by Walshe (1944) a heredo-familial disease characterised by wasting of the digital muscles of the limbs, of sternomastoids and of certain facial muscles by a peculiar delayed relaxation of certain muscles (myotonia) by testicular atrophy baldness, cataract and mental deterioration'

MYASTHENIA GRAVIS

In myasthenia gravis, which is pharmacologically the opposite of myotonia, thiopentone can produce effects similar although less pronounced, than those described above. This sensitivity is due to the action of thiopentone on an abnormally sensitive myoneural junction.

While patients with myasthenia gravis who come to operation vary greatly in the severity of their symptoms and in their response to neostigmine, it is usually possible to perform oral intubation with doses of thiopentone of the order of one-quarter to one third of that required in normal persons. The conditions produced for laryngoscopy by thiopentone alone are comparable with those which one would expect if the drug were followed by suxamethonium. Abdominal relaxation also resembles that seen in curarised patients, and controlled respiration can be easily performed if required. The duration of thiopentone narcosis is not prolonged in myasthenic subjects.

One must be prepared for a period of respiratory depression lasting up to 15 to 20 minutes if a normal dose of thiopentone

is given to a patient with severe myasthenia gravis. Where the operation is for removal of the thymus gland, this is not a serious mishap, as a cuffed endotracheal tube will be passed in any case, lest the pleura be opened during the splitting of the sternum. However for minor procedures, such as opening of abscesses, only sufficient of the drug should be given to produce loss of consciousness and maximum use made of agents which have no effect on the myoneural junction, such as nitrous oxide and trichlorethylene. It must be remembered that these patients are abnormally sensitive to *d* tubocurarine, gallamine triethiodide and laudexium, but react normally or are slightly resistant to the depolarising relaxants. The curarising action of the ethers should also be remembered, and unless respiratory depression is desired it is better to avoid the use of these drugs.

POTASSIUM INTOXICATION

The dangers associated with the use of thiopentone in this condition are due to the ease with which hypercarbia can occur during or following its administration. Sealy Young and Harris (1954) have demonstrated that the inhalation of carbon dioxide results in a rapid increase in the plasma potassium level. A further sharp rise occurs if the carbon dioxide is suddenly withdrawn; this is often associated with serious changes in the electrocardiogram and even with ventricular fibrillation. The latter rise in the potassium level may be associated with a sudden release of adrenaline, which may be the cause of the fibrillation.

While rises in the plasma potassium to toxic levels are unlikely to occur following the use of thiopentone in normal patients, dangerous levels may well be reached in subjects who already have a raised plasma-potassium level. This can occur after the rapid transfusion of large quantities of stored citrated blood in patients whose renal function is impaired, after the release of large quantities of potassium from ischaemic muscle and in various electrolyte disturbances. In such conditions respiration should be aided or controlled if there is any suggestion of respiratory depression following the use of thiopentone. Controlled respiration should be used as a routine if a muscle relaxant has been used, irrespective of the dose.

If prolonged respiratory depression has been allowed to occur

inadvertently, the alveolar carbon dioxide should not be suddenly reduced. This also applies when laryngeal spasm has occurred after the induction of anaesthesia or after difficulty in intubation in the presence of apnoea due to suxamethonium. Sealy *et al* have found that an adrenolytic agent, benzodioxane (piperoxan), diminished the rise in plasma potassium that followed the withdrawal of carbon dioxide. This agent, or drugs with the same action, may be of value in the circumstances mentioned above. The intravenous administration of 10 to 20 per cent. glucose and insulin is another effective method of reducing the plasma potassium to normal levels. It is interesting to note that Robbins and Pratt (1936) found that ether significantly decreases the blood levels of potassium and its use seems to be indicated in conditions of potassium intoxication.

MISCELLANEOUS

In **anaemic patients** it must be remembered that the effects of respiratory depression and hypoxia will not become apparent as readily as in normal subjects. The myocardium may be affected by the anaemic hypoxia and thus rendered more sensitive to thiopentone. Futhermore, an adequate oxygen supply to vital structure such as the brain and heart may only be maintained in the presence of an adequate blood pressure during consciousness by an increased circulation rate. Care should thus be taken to minimise the depressant effects of thiopentone on the cardiovascular system. The increased duration of action with the drug in patients with a low haemoglobin content of blood has already been discussed (p. 135) but this is no deterrent to the use of thiopentone provided the total dose is suitably adjusted.

The dose of thiopentone which will be required to produce a satisfactory degree of anaesthesia in **drug addicts** may be such as to have a marked depressant effect on the circulation, since in these patients resistance is acquired only to the narcotic effects of the drug. As shown in a previous case-report, drug addiction also increases tolerance to competition blocking relaxants. Since prolonged administration of sedatives and analgesics reduces the pseudocholinesterase, such patients should be sensitive to suxamethonium, although there are no clinical reports published to substantiate this hypothesis. Anaesthesia in such persons can be

most easily achieved by allowing them to have whatever drug they are taking in the dose to which they are accustomed, together with *atropine or hyoscine*, in place of the unusual premedication. This cannot be applied to chronic alcoholics, in whom the premedication should be increased, preferably with drugs which have little effect on respiration such as pethidine a combination of promethazine and chlorpromazine or a barbiturate.

Diabetics who are stabilised on soluble insulin present *no difficulty* as far as the administration of thiopentone is concerned, as the drug in *moderate doses* has an insignificant effect on the blood-sugar levels. The meal prior to operation should be replaced by glucose of an equal calorie value (which is preferably given intravenously) and the requisite dose of insulin. Where a long acting or slowly absorbed insulin preparation is being used, it should be changed to soluble insulin for a few days before and after operation. The uncontrolled diabetic presents a problem which is the same whatever the anaesthetic used. The danger is increased if the stage of ketosis with vomiting has been reached. A 5 to 10 per cent. dextrose drip should be set up immediately The rate of administration of this and the accompanying dose of insulin will depend on the blood-sugar level. Unless the operation is of extreme urgency as in the case of uncontrollable haemorrhage or a perforated viscus, a reasonable reduction in the blood sugar and the ketosis should be aimed at before induction of anaesthesia. During operation, thiopentone/nitrous oxide/oxygen and thiopentone/cyclopropane with or without muscle relaxants have the least deleterious effects on glucose metabolism, provided hypoxia is avoided. *The observation of Griffiths (1953)* that hexamethonium induces hypoglycaemia and potentiates the action of insulin under general anaesthesia must be remembered, and hypotension inducing drugs are better avoided in diabetics unless facilities are available for repeated blood-sugar estimations.

In **vagotonic subjects** there is often an increased tendency to laryngeal spasm after the use of thiopentone. Such patients frequently have a labile blood pressure or slight hypotension and are more prone to severe falls in blood pressure after the rapid injection of the drug Most children fit into the above category which includes patients with peptic ulceration. The above remarks are often stated to apply to patients with red hair although there is no scientific basis for this view Effective atropinisation,

slow injection of thiopentone and the judicious use of pethidine and suxamethonium can overcome the difficulties which are encountered in vagotonic subjects.

In patients with **phaeochromocytoma** the induction of anaesthesia with thiopentone frequently evokes a hypertensive attack. This is more likely to be due to apprehension, temporary hypoxia or mild hyper or hypocarbia rather than to any specific effect of the drug although the author has observed its occurrence after a supplementary dose of thiopentone in a patient whose respiration was already manually controlled. Hypoxia must be avoided at all costs during the induction stage in these patients and if hypertension does occur hyperventilation should be carried out with a large flow of gases. Anti adrenaline drugs such as benzodioxane (piperoxan) or Rogitine should be readily available, and a needle left in a suitable vein for their intravenous injection if the hypertension does not rapidly subside.

Patients with **Addison's disease** are very susceptible to thiopentone, and induction of anaesthesia may be followed by an Addisonian crisis. Prolonged narcosis may be due to hypotension and extracellular dehydration interfering with diffusion of thiopentone, or more likely to hypoglycaemia. The author (1951) encountered a patient who came to operation for the insertion of a D O C.A. implant and in whom 400 mg thiopentone produced unconsciousness for 2¼ hours and drowsiness for a further 10 hours. Eighteen hours after operation the blood pressure was 85/50 and in spite of an infusion of 1 litre of 5 per cent. dextrose in normal saline the blood-sugar level was only 75 mg per cent. Unless there is a history of sensitivity to local analgesics general anaesthesia is better avoided in patients with Addison's disease.

Minor degrees of **supra-renal insufficiency** are sometimes detected in patients who are to be operated on for a completely unrelated condition. If the nature of this is such that general anaesthesia is essential supra renal cortical extract should be given before operation and extreme caution exercised with the use of thiopentone to prevent hypotension Eschatin in 5 ml. doses can be given intravenously during anaesthesia, and if consciousness is not regained within the expected time the possibility of hypoglycaemia should be considered. There is some evidence that patients who are receiving cortisone or A.C T H. therapy behave in a manner similar to that just described. Until more is

CHAPTER VII

HAZARDS ASSOCIATED WITH THE USE OF THIOPENTONE

Mortality Rate. It is impossible to assess accurately the incidence of fatalities which can be attributed to the use of any one anaesthetic agent. Most deaths are not recorded in the literature, and many published series either do not mention the mortality rate or fail to differentiate between deaths due directly to the anaesthetic and those from other causes. A search of the literature revealed 48 publications dealing with the routine use of thiopentone in which the deaths attributed to the drug were recorded. These, together with 4 series contributed by individual anaesthetists, deal with over 135 000 administrations of the drug. To this number can be added some cases from the formidable report by Beecher and Todd (1954) *on deaths associated with all* anaesthetics. An analysis of the total figures (Table XLI) reveals

TABLE XLI

Representative figures showing the approximate mortality due to thiopentone

	52 Published and Unpublished Series	*Beecher and Todd (1954)*	*Total*
Total number of administrations	135,281	57,000	192,281
Death attributable to thiopentone	44	23	67
Incidence	1 : 3072	1 : 2470	1 : 2870
Source of Cases			
United States	101 060	57,000	158,060
Great Britain	14,677	—	14,677
Canada	7,583	—	7,583
Military	3,762	—	3,762
Others	8 199	—	8,199

that, *out of 192,281 administrations of thiopentone*, 0·035 per cent. resulted in a fatality which was directly attributable to the drug

The exact cause of death in the above cases, excluding those of Beecher and Todd for which details are not given, are classified in Table XLII It will be seen that where this information is

TABLE XLII

Exact cause of death in 44 cases (from Table XLI) after the use of thiopentone

Circulatory failure		13
Immediately after injection	9	
Overdose in shock	4	
Respiratory obstruction		5
During operation	4	
Immediately post-op	1	
Prolonged hypoxia		3
During operation	2	
After operation	1	
Unspecified		23

available, the largest number (62 per cent.) was due to circulatory failure. In the report by the Committee of the Association of Anaesthetists of Great Britain and Ireland, which studied 232 deaths associated with anaesthesia, the use of thiopentone followed by immediate cardiovascular collapse formed the second largest group (21 per cent.) (*Anaesthesia* 1952) If from these 232 deaths are selected those in which there was one fairly clear-cut cause (160) then thiopentone was responsible for almost one-third of this total. There may have been deaths classified under respiratory obstruction during and after operation for which an overdose of thiopentone could be held responsible.

It would be misleading to attempt to compare the number of fatalities due to thiopentone with those attributable to other agents as one cannot tell the relative incidence of administration of the various drugs. It can be assumed that the large total due to thiopentone is at least in part due to its widespread use during induction of anaesthesia.

Although a mortality rate of 1 in 2870 has been found in almost 200 000 administrations of thiopentone, it does not follow that one need encounter 3 to 4 inevitable deaths in each ten thousand administrations of the drug No details of dosage, rate of injection or of the pre-operative condition of the patients are available for

the fatal administrations, but it is possible that many fatalities could have been prevented by the judicious use of the drug and a proper appreciation of its limitations. Circulatory failure is always due to overdosage, and respiratory obstruction and prolonged hypoxia are likely to result from the same cause. The higher incidence of the former is only an indication that an over dose of thiopentone is most likely to cause death through its depressant effects on the cardiovascular system, and that its effects on this system are less easy to counteract than its action on respiration.

Theoretically there should be no inevitable death rate with thiopentone if its limitations are understood and if all anaesthetists are highly skilled. Such skill only comes from experience in using the drug, and considering the ease with which an overdose of an intravenous anaesthetic can be given, the reported mortality may even be taken as a tribute to the safety of thiopentone.

No mention has been made of the non fatal accidents which may follow the use of thiopentone, and it is impossible to assess the morbidity attributable to the drug. Every intravenous injection carries certain risks which are increased when a highly irritant substance such as thiopentone is injected. It is proposed to discuss even the minor hazards which are associated with intravenous anaesthesia and offer suggestions for prophylaxis and treatment. The sequelae of these are often forgotten, and many patients suffer from a sore arm for some time after an 'uneventful' administration of thiopentone.

DANGERS OF ANY INTRAVENOUS INJECTION

Infection. There is a slight risk of both generalised and localised infection from any injection. Organisms may be introduced into the blood stream from syringes or needles which have been contaminated by the anaesthetist or his assistants, or by cross infection from patient to patient. Infection at the site of puncture is particularly likely to occur if extravasation of blood has followed withdrawal of the needle or if thiopentone has been deposited in the subcutaneous tissues. Apart from the possibility of cross-infection, these complications can be minimised by an aseptic injection technique. The skin should be cleaned with cetrimide

followed by spirit, and allowed to dry, and the needle should not be handled except at the butt.

The danger of cross infection applies particularly to intravenous injection because of the aspiration of blood into the needle and syringe. Bigger (1943) and Sheehan (1944) have shown that hepatitis attributed to intravenous arsenicals was in fact due to a virus transmitted by unsterile syringes. The incidence of carriers of the virus among blood donors has been placed as high as 0 5 per cent. (*Brit med J*, 1950) The risk is still present even when blood is not aspirated into the syringe since Hughes (1950) found erythrocytes in the fluid of the nozzle of the syringe in 14 per cent. of cases after intramuscular injection

Needles and syringes should always be thoroughly cleansed and sterilised after each case. Complete bacteriological sterility can be achieved only by sterilisation in a hot oven or an autoclave (M R.C., 1945) Boiling in water will destroy all pathogenic bacteria except those producing resistant spores which can be killed by the addition of sodium bicarbonate to the water Care must be taken in using sodium bicarbonate, for, while the resulting alkalinity will not decrease the potency of the thiobarbiturates, it may affect other drugs used in anaesthesia, particularly pethidine and some local analgesics. Chemical disinfectants, on the whole, are unsatisfactory for sterilisation of syringes. For details of methods of cleaning and sterilisation of syringes see Appendix 5

Haematomata. These are particularly common in subjects with a sparseness of subcutaneous fat, or in elderly patients with tortuous and sclerotic veins. Leakage of blood from vessels is more liable to occur in any patient if the venous tourniquet is not released before removal of the needle.

The risk of haematoma formation can be reduced by a proper venipuncture technique. In patients with tortuous mobile veins, injection should be made at the junction of two vessels. The needle, after insertion through the skin, should run for a short distance in the subcutaneous tissues before puncturing the vessel. This produces a valvular effect when the needle is removed, the intact skin over the site of the puncture preventing leakage of blood. Firm pressure over the point of entry of the needle has a similar effect and temporarily raising the arm above the suprasternal notch, thereby reducing the venous pressure, is probably the most valuable procedure of all. If pressure is

applied proximal to the site of puncture of the vessel, the resultant venous stasis will aid the formation of a haematoma. Acute flexion of the arm after withdrawal of the needle may have a similar undesirable effect.

Haematomata are seldom large enough to necessitate any active treatment. However there is a remote possibility of an undue collection of blood embarrassing the blood supply to the limb In such cases an incision may be necessary to relieve the tension. An injection of hyaluronidase may help to dispel the blood, but strict asepsis is essential since blood clot is a very suitable medium for the growth of organisms.

Broken Needles. Fortunately this generally occurs at the butt of the needle and the broken part can be easily removed. It is recommended that the needle should not be inserted right up to the butt. Breakages of the tip of the needle are more serious. The broken part should be located by X ray and an immediate attempt made to remove it, if it is still in the arm.

The use of eccentric nozzled syringes reduces the strain on the needles and minimises the likelihood of breakage. Movement of the limb must be avoided during injection. As pointed out previously the incidence of this occurring during the induction of anaesthesia is lessened when the patient has been premedicated with an analgesic drug (see page 70)

DANGERS ASSOCIATED WITH THIOPENTONE

These can be classified as follows

1 **Local Effects** due to the irritant properties of the drug
   - (*a*) Tissue damage resulting from extravenous injection.
   - (*b*) Sequelae of intra-arterial injection.
   - (*c*) Venous thrombosis.
   - (*d*) Nerve lesions.

2 **General Effects,** most often associated with the misuse of thiopentone.

Respiratory System

Apnoea—respiratory depression.
Obstruction muscular relaxation,
laryngeal or bronchial spasm,
loss of protective mechanisms—aspiration of fluids or solids.

CARDIOVASCULAR SYSTEM

Immediate toxic effects—cardiovascular collapse.
Effects secondary to hypoxia due to respiratory insufficiency
" " hypercarbia,
" , prolonged hypotension
" blood loss,
" " manipulations by the surgeon.

CENTRAL NERVOUS SYSTEM

Delay in return of consciousness.
Sequelae of hypoxia.
Sequelae of cardiovascular effects.
Post-operative mental impairment.
Post-operative restlessness.

3 Delayed Toxic Effects

(a) Hepatic dysfunction.
(b) Sequelae of prolonged hypoxia or prolonged hypotension
(c) Attacks of acute porphyria.
(d) Addisonian crisis.

4. Not directly due to Thiopentone but frequently associated with its use.

(a) Mechanically produced nerve lesions, most commonly involving the brachial plexus.
(b) Skeletal injuries, due to lack of care in positioning or transferring patients, especially in osteoarthritics.

LOCAL EFFECTS

The extravaneous injection of thiopentone results in local tissue irritation. The extent of the damage depends on the concentration and total amount of the drug injected outside the vein. Patients with a poor peripheral circulation or with sparseness of subcutaneous tissues are more susceptible to the irritant effects of thiopentone. The clinical effects can vary from temporary slight tenderness at the site of injection to extensive tissue necrosis. The irritant action is enhanced by pressure from the injected fluid and spasm of vessels caused by the high alkalinity of thiopentone.

The prophylaxis consists of aspiration of blood before the initial injection. Where the needle point is buried deep and localised swelling not easily detectable, one must obtain a good flow of blood before injection, as a small amount may result from the passage of the needle tip through the vessel or the aspiration of a haematoma. Except where the vessel is large and clearly visible

aspiration is also important each time a syringe is changed as the movement may be sufficient to dislodge the needle from the vein. A dilute solution of thiopentone (not exceeding 2.5 per cent.) should be used in the absence of easily visible veins. This will reduce the intensity of the tissue reaction if inadvertent extra-venous injection should occur

Procaine has the dual effect of relieving the pain and producing vasodilatation. It should always be injected into the tissues where there is any suspicion of an extravenous injection and it may with advantage be combined with hyaluronidase, which aids the dispersion and dilution of thiopentone. Where immediate treatment has not been instituted and where tissue necrosis seems a possibility the limb should be immobilised and local heat applied to the affected area. Intensive chemotherapy should be given to prevent a spreading cellulitis. Incision to relieve tension or release pus, or excision of a slough may be necessary in severe cases. Skin grafting may be required later to eliminate reduction of movement.

It is not generally appreciated that in patients who have a paucity of visible veins less time will be wasted, and less discomfort caused to the patient, by a proper inspection of all possible sites of injection the application of heat to the limbs and the use of a proper venous tourniquet for 2 to 3 minutes (a sphygmomanometer cuff is probably the best). Flicking the vein with the fingers is often of help If intermittent injections are to be used, a narrow bore non-clotting needle should be inserted. It is worth remembering that it is extremely rare not to find a suitable leg vein about 1 cm. in front of the internal malleolus.

Although most patients now expect to be put to sleep by the needle there is no justification for making repeated futile attempts at venipuncture and depositing a small amount of thiopentone at various points over the limbs. This applies particularly to subjects who are having minor operations A word of explanation to the patient is all that is necessary to enable an easy nitrous oxide/oxygen induction to be carried out, and following this with cyclopropane and oxygen or adding trichlorethylene to the nitrous mixture does not result in prolonged narcosis Even in major surgery where the use of muscle relaxants may be essential cyclopropane and oxygen will quickly produce a marked peripheral vasodilatation, facilitating venipuncture. Cyclopropane is rapidly

eliminated and a non-explosive mixture, with thiopentone as basal narcotic, can be given after induction, if required. There is a strong belief in some quarters that to abandon the intravenous method of induction of anaesthesia because of unsuitable veins is admitting defeat. This belief however, in no way conforms to the essential practice of 'fitting the anaesthetic to the patient'"

The dangers of **intra-arterial injection** of thiopentone have been pointed out by many writers the most notable of the early contributions on this subject being those of Macintosh and Heyworth (1943) and Cohen (1948) The latter has placed the incidence of this accident at between 1 8000 and 1 55,000 This seems a gross underestimation, since data collected by the author from various anaesthetists (dealing with over 31 000 anaesthetics) reveal one intra arterial injection in about every 3500 administrations of thiopentone. No serious permanent sequelae occurred in the cases of this survey and no figures are available to show how frequently intra arterial injection may produce permanent disability

Since most intra arterial injections result from the use of vessels in the antecubital fossa, it is advisable to consider how such injections may be made. The two main contributory factors are (*a*) absence of arterial pulsation and (*b*) anatomical variations at the elbow

(*a*) Arterial pulsation may be obliterated by the venous tourniquet, or as pointed out by Cohen, in a high percentage of normal persons bracing the shoulders will lead to compression of the subclavian artery by the clavicle against the first rib and loss of distal pulse a sandbag between the shoulders may act similarly In some patients rotation of the head or hyperextension of the neck will lead to a compression of the subclavian artery and obliteration of the brachial pulsation. Elevation of the arm in full abduction often obliterates the pulse the axillary artery is believed to be compressed or angulated over the root of the coracoid process or over the tendinous insertion of the pectoralis minor muscle. There may be complete absence of arterial pulsation in hypotensive states.

(*b*) The brachial artery divides above the elbow in about 10 per cent. of persons, and in one third of these this peculiarity is bilateral. When the division is high the ulnar artery almost invariably reaches the distal part of the arm by passing superficial to the flexor group of muscles. In its downward path it may hug the radial artery in the elbow area, but at times it takes a medial sweep and the two vessels may lie well apart. In its downward superficial course the ulnar artery may occupy

one of three positions (1) subfascial all the way down (2) subcutaneous in the elbow and then *passing below the deep fascia* (3) subfascial in the upper part of the forearm, then subcutaneous and finally subfascial again in the distal third of the forearm. When the ulnar artery is superficial at the elbow its anterior interosseous branch comes off *the radial division. The superficial ulnar vessel is also usually* smaller than normal and compensatory enlargement is invariably found in the radial. Such superficial ulnar vessels are derived from the vasa abberentia and, like other superficial vessels, have a fuller nerve supply than have the deeper branches consequently they are more readily thrown into spasm.

Hypertension of the elbow straightens the normal tortuosity of the brachial artery and makes injections easier Pulsation of superficial arteries may not always be visible, especially in young healthy persons, but, unless the brachial artery is compressed as described above, the pulsations are always easily palpable.

Thiopentone is a strong alkaline irritant and its intra-arterial injection can cause spasm of the vessel. Distension of the arterial wall from rapid injection may be a contributory factor The intima of *arteries appears to be particularly susceptible* to thiopentone and thrombosis readily occurs after its injection. The likelihood of this is increased if the thiopentone has been trapped in the arterial tree by vascular spasm or occlusion of the circulation due to any of the causes already discussed. Thrombosis may develop insidiously and complete occlusion with obliteration of the pulse has been recorded as long as 10 days after the first aggregation of platelets over the damaged site. The thrombosis usually extends proximally as far as the origin of the major collateral vessel above the site of the arterial puncture.

The *distal forearm and fingers are affected according* to the distribution of the thiopentone. Shunting of the drug into the skin may result in discolouration or even sloughing In muscles it will cause gross oedema, and thrombosis of a major vessel will result in ischaemia and death of the muscle. Gangrene of the fingers results from complete blockage of their blood supply but it is not unusual to find only the distal portions involved. Cohen (1948) suggests that this is due to intense spasm of the arterio-venous anastomosis followed by clotting in the venous loop Ischaemia of nerves may result from impairment of their blood supply due *either* to thrombosis or to pressure from oedema of the surrounding muscles.

The end result of intra-arterial injection depends on a large

number of factors, of which the following seem to be the most important.

(*a*) The concentration and amount of solution injected. More concentrated solutions are more irritant. This view is substantiated by Table XLIII, which analyses sequelae of 46 intra-arterial injections of thiopentone, some of which have been described in the literature. (It must be pointed out that Table XLIII makes no allowance for other factors, to be outlined later

TABLE XLIII

The sequelae of intra-arterial injection of thiopentone related to the strength of solution used

Percentage Solution	*Number of Cases*	*Permanent Sequelae*		
		Nature	*No. of Cases*	*Percentage*
10	11	Amputation required Gangrene of fingers Skin slough Nil	5 3 1 2	45 28 9 18
5	16	Amputation required Skin slough Area of hypoaesthesia Nil	3 1 1 11	19 6 6 69
<5–>2·5	5*	Nil	5	100
2·5 or less	14	? slight hypoaesthesia Nil	1 13	7 93

* Three of these patients received a thiopentone-curare mixture and the histamine-like action of the intra-arterial injection of curare (Comroe and Dripps, 1946) must be remembered.

and is not presented as scientific evidence of the greater dangers of concentrated solutions.) The larger the total dose of thiopentone injected, the less will be the dilution in the peripheral vascular tree.

(*b*) Rate of injection The more the vessel is distended the greater will be the spasm.

(*c*) Nerve supply to the punctured vessel. The richer the network of nerves on the vessel, the more sensitive it will be to irritants and hence the greater the chance of spasm.

(*d*) State of the arterial circulation at the time of the injection

If this is sluggish or completely occluded, thiopentone will remain longer in contact with the intima and increase the danger of thrombosis. The retrograde spread of the solution will also be greater where the flow of blood is occluded. If the arterial blood flow is rapid, there is a greater chance of thiopentone being well diluted before reaching the terminal arterioles.

(e) Distribution of thiopentone in the limb This determines whether the main damage affects the skin, muscles or nerves.

(f) Rapidity of relief of vascular spasm.

(g) Efficacy of later treatment.

One might expect a gush of blood into the syringe when an artery is punctured, but this rarely occurs. Pulsations of the vessel may be transmitted to the needle, but it is doubtful if these are ever as marked as to be appreciated by the administrator Aspirated arterial blood is a brighter red than venous blood, but this difference in colour is marked by the yellowish thiopentone. These considerations show that under normal conditions arterial puncture can be easily mistaken for venipuncture. As mentioned previously inspection of the limb will usually not distinguish between the two vessels (Fig 43) and the absence of pulsation or palpitation is the most reliable means of ensuring that the needle is not in an artery

The immediate clinical signs of intra arterial injection of thiopentone can often be detected with amounts of the drug which are too small to produce any permanent damage. Pain shooting down the forearm, is the commonest early sign and is agonising in nature. It is frequently accompanied by movement of the arm or an attempt by the patient to remove the syringe and needle. Cohen mentions descriptions of it by patients such as like boiling water being poured over my hand and the hand felt like a flaming branch The most dramatic description of this pain ever elicited by the author from a patient was like ice-cold water running down my arm and freezing on the tips of my fingers as icicles which dropped off after a minute or two The agonising nature of this pain is such that it cannot be simulated by any other incident during the injection of thiopentone. Unless aware of the possibilities, pain may be attributed to apprehension during the induction period. In one case thiopentone was inadvertently injected into an artery to induce anaesthesia for Caesarian section in a woman who had been in labour for some time. The cry

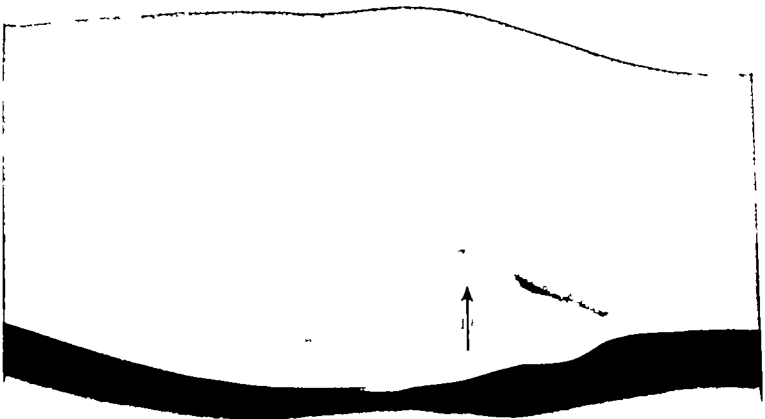


FIG 43.—Veins distended with rubber band. Arrow indicates superficial ulnar artery. Gliding of needle to enter medial basilic vein may lead to puncture of the artery (Cohen 1948)

(Facing p. 200)

which followed the injection was attributed to the onset of a uterine contraction Incidents like this must be exceedingly rare

Unfortunately, in an occasional patient no pain may follow the intra arterial injection of thiopentone, as shown by a recent medico-legal case (*Brit med J*, 1951)

After the intra arterial injection of a small volume of dilute thiopentone, the pain in the arm may subside after a few minutes, but with larger amounts it may persist for several hours Patients in whom anaesthesia is continued with another agent may still complain of the pain on the return of consciousness A rarer occurrence is for the pain to disappear shortly after the injection and return later This sequence may be repeated several times and is presumably due to intermittent attacks of vascular spasm

The intense arterial constriction after injection is manifest by an immediate disappearance of the radial pulse and blanching of the limb Because of the increased time taken for the anaesthetic to reach the central nervous system the onset of unconsciousness will be slightly delayed Severe vasomotor collapse may occur and the resulting hypotension may be taken as the explanation for the inability to palpate the peripheral pulse. Where the arterial blood flow to the forearm is rapidly restored blanching of the limb will be followed by reactive hyperaemia Oedema of the limb occurs quickly where the muscles have been invaded by thiopentone and mottled patches and ecchymoses indicate skin involvement.

Where spasm of digital or main vessels persists or where immediate thrombosis occurs the blanching is followed by increasing cyanosis of the affected part, which becomes a dark purple colour and is followed by gangrene Cohen (1948) has observed that fingers which developed gangrene did not show oedema and fingers which recovered did The absence of oedema indicates that the circulation in these fingers must be completely arrested and the major digital vessels thrombosed. Extensive oedema of the muscles usually results in flexion of the fingers. It is believed that muscles cannot stand complete ischaemia for more than six hours, and failure of the oedema to subside within this time usually means that the chance of saving the limb is small.

Since the main nerves of the forearm receive their blood supply from the radial and ulnar arteries interference with the flow in the latter may lead to loss of sensation The interosseous branch

of the ulnar artery is particularly important, as it supplies the median nerve, but where there is a high division of the brachial artery this branch is usually given off by the radial. Consequently it will not be affected unless there has been retrograde spread of the thiopentone.

It follows that the sequelae of an intra-arterial injection of thiopentone can vary from transient pain to gangrene of the forearm. While some idea of the prognosis can be gained from the factors discussed on page 199 there are no means of forecasting accurately the ultimate result, and all cases must be treated immediately without delay The suggested lines of treatment are as follows

(a) Dilution of injected thiopentone.
(b) Relief of arterial spasm and pain.
(c) Prevention of thrombosis prevention of spread of thrombosis and/or extraction of clot.
(d) Later symptomatic treatment.

Dilution of the thiopentone applies particularly in cases where there is some obstruction to the arterial flow to the limb The cause should be sought for and remedied, the tourniquet should be checked to see that it has been completely released, tight clothing or bandages cut, rotation of the head or hypertension of the neck corrected and the affected shoulder slightly raised. The needle is left in the vessel and 10 to 20 ml. 0 5 per cent. procaine injected slowly This has also some vasodilatating action, and is mentioned before the more effective vasodilator papaverine because of its more ready availability in the anaesthetic room. If neither of these two drugs can be procured quickly normal saline, slightly warmed if possible, should be injected. Papaverine should be given in doses of 40 to 80 mg in 10 to 20 ml. saline.

Where the needle has been removed from the vessel, reinsertion may be difficult, and in this case either procaine or papaverine should be infiltrated around the site of the puncture. Anaesthesia should be continued with a vasodilator drug preferably cyclopropane and oxygen.

Immediate and fairly prolonged relief of pain can be achieved by performing a brachial plexus block with 0 5 per cent. lignocaine. If sufficient of this drug is deposited along the back of the first rib the stellate ganglion will also be blocked, and these two procedures

help to open up the collateral circulation During the performance of a brachial plexus block it is an easy matter to puncture the subclavian artery (which lies adjacent to the scalenus anterior muscle) and inject further papaverine. This is preferable to making repeated attempts to puncture a vessel which is in spasm.

The immediate injection of heparin into the affected artery has been suggested and is a valuable procedure but its use precludes the immediate performance of any operation which necessitates a skin incision and makes brachial plexus block a hazardous procedure. There should be no hesitation in postponing any operation which is not extremely urgent, and in this case 20 000 units of heparin should be injected into the subclavian artery A long acting anticoagulant of the dicoumarol type should be given orally and heparinisation continued until this takes effect, usually within 24 to 48 hours. Control of dosage by haematological investigations will be necessary The dangers of the indiscriminate use of heparin is shown by the following case (Cohen 1955)

Following the intra arterial injection of thiopentone into the *right* arm, heparin therapy was instituted. On the *left* arm there was a fractured radius, and after manipulation the arm was placed in plaster Extensive bleeding into the *left* arm followed and led to muscle death.

Each case must be considered individually regarding the necessity for repeating any of these procedures. The return of pain is an indication for repeating the brachial plexus block and injecting papaverine. Sedation should be with drugs which relax vascular tone such as the barbiturates and pethidine morphine should not be given.

If decided upon, surgical treatment must be carried out within six hours of the injection. Protamine must be given to heparinised patients before the operation Cohen (1948) recommended incision of the vessel and extraction of the clot. The artery should preferably be opened well proximal to the injection site so that the ultimate suture will not lie within the damaged area. The clot may be extracted with forceps or by aspiration, and Cohen mentions that if exploration is not early the clot may be adherent to the vessel wall and not be removable by suction. In this type of case incision of the vessel in two of its distal branches will allow removal of the clot by proximal syringing and suction. A distal intra arterial injection of heparin should always be given at

the time of operation The artery wall must be "packed with papaverine during and after operation

Other suggested lines of treatment include attempting to force the opening of the collateral circulation by immersion of the opposite limb in hot water or by using a heat cradle over the rest of the body The affected limb should be elevated to assist both venous and lymphatic drainage, but it should not be raised above the heart level. Since cooling causes vasoconstriction, the damaged limb should be wrapped in a sterile towel and covered with wool, but it should not be overheated.

Late symptomatic treatment depends on the outcome of the earlier measures. Chemotherapy and anti-gas gangrene serum should be given to prevent the spread of cellulitis from gangrenous muscles. Amputation of digits tendon transplantation or even amputation through the forearm may eventually be necessary

Various suggestions have been made for the prevention of intra arterial injection during the induction of thiopentone anaesthesia. The most important of these are avoidance of vessels in the ante cubital fossa, palpation of injection site before application of the tourniquet, and the injection of 1 to 2 ml of solution followed by a pause to see if the patient develops pain. If no suitable vein can be found outside the antecubital fossa, the radial side is preferred to the ulnar In the case of the latter the only certain way of being sure that the injection will not be given into an artery is to set up an intravenous drip and inject the solution through this. Even the radial artery can take an aberrant course at the wrist, and gangrene of the thumb and index finger has followed the injection of thiopentone into such a vessel (Cohen, 1955). A vein which overlies an artery is not altogether safe, as under these circumstances intravenous injection of an irritant can cause arterial spasm. Other points which are worthy of mention are avoidance of factors which interfere with the arterial blood flow avoidance of rapid injection and the use of a 2 5 per cent. solution, which appears to be followed by a lower incidence of untoward sequelae than a 5 per cent. If a series of repeated injections is contemplated during the operation, either an intravenous drip should be set up or a non blocking needle inserted before induction of anaesthesia, as in an unconscious patient pain following injection cannot be elicited and a more likely cause

may be sought for disappearance of the radial pulse than intra arterial injection.

Venous thrombosis is rarely reported after the use of thiopentone and occurs more commonly with the 5 per cent. than after the 2 5 per cent. solution. On theoretical grounds it should be more common where continuous or intermittent injections have been made into one vessel The thrombosis becomes evident a few days after the injection and may be extensive, involving the deep veins by retrograde flow Hewspear (1945) has described a case where deep venous thrombosis followed the injection of thiopentone. He attributed this result partly to the fact that the elbow was placed in acute flexion after the injection. Cohen (1948) has seen an injection of thiopentone which was followed by an enormous oedematous forearm which took 9 months to subside. The author has heard of a lesser degree of oedema following the intermittent injection of 5 per cent. thiopentone (to a total of 1 2 g) where full recovery took 4 to 5 months. In this patient the lower limb up to just below the knee was involved as, save for the initial dose of 350 mg the internal saphenous vein was used for the injection There may be some similarity between this and Hewspear s case as the leg was con stricted between a rubber cushion and a tight strap over the lower thigh. It would seem that trapping the solution in the vein may be an important factor in the aetiology of venous thrombosis, and for this reason the common practice of acute flexion of the elbow after injection is to be deprecated.

The exact danger of venous thrombosis after thiopentone is not known. Cohen (1948) thinks that it may well lead to loss of a limb since this is known to have followed the accidental injection of sclerosants into the deep veins of the leg Venous obstruction alone may lead to muscle death, and while the picture is somewhat different from that seen after thrombosis of a main artery the end-result is the same. Various writers have commented that when the arterial circulation is poor or in spasm, the onset of venous thrombosis may seal the fate of the limb For this reason, should intra arterial injection be suspected, it would be unwise to inject any further thiopentone into the limb and run the risk, however small of thrombosis.

The injection of thiopentone into nerves is not usually listed as a hazard of intravenous anaesthesia. On considering the

relevant anatomy, it seems surprising that more cases have not been reported.

The median nerve enters the antecubital fossa just medial and slightly superficial to the brachial artery and enters the forearm between the deep and superficial heads of pronator teres. Here it crosses the ulnar artery being separated from it by the deep head of pronator teres. In the antecubital fossa it is covered by the bicipital fascia which separates it from the superficial veins. Higher up in the arm it lies immediately deep to the basilic vein. The nerve to pronator teres usually arises above the elbow and in the forearm the median nerve gives branches to the superficial muscles with the exception of flexor carpi ulnaris. The anterior interosseus nerve arises as the median nerve passes between the heads of pronator teres and it accompanies the anterior interosseus artery along the front of the interosseus membrane of the forearm. It supplies flexor pollicis longus, half of flexor digitorum profundus, sends branches to the deep surface of pronator quadratus and ends by supplying the wrist joint.

The sensory distribution of the median nerve consists of most of the palm with the exception of the outer border of the thenar eminence and a strip along the medial border It supplies the anterior surface of the thumb index and middle fingers and the lateral half of the ring finger On the back of the hand its distribution is limited to the thumb and the distal half of the same fingers that it supplies on the anterior surface.

The anterior branches of the medial cutaneous nerve of the forearm passes usually in front, but occasionally behind, the median cubital vein. It descends on the front of the medial side of the forearm and supplies the medial half of the anterior surface of the forearm from the antecubital fossa to just above the wrist.

The lateral cutaneous nerve of the forearm passes deep to the cephalic vein and descends along the radial border of the forearm, to the wrist. It supplies the skin over the lateral half of the anterior surface of the forearm and distributes branches which run round the lateral border to communicate with the posterior cutaneous nerve of the forearm and the terminal branches of the ulnar (Johnstone and Whillis, 1946.)

Pask and Robson (1954) have demonstrated the ease with which the median nerve can be injured during injection in the medial aspect of the antecubital fossa. They have shown that there is no basis for the belief that the direction of the needle to make an injection into the median nerve must be much more nearly perpendicular to the axis of the arm than if the basilic vein is the objective. Pask and Robson therefore consider that if an injection *must* be made at this site, accidental damage to the median nerve could occur by mischance even though prudence were exercised.

A slight movement of the patient might advance the needle, at first satisfactorily placed in the vein a very short distance, so that its point lies against the nerve. The change in position would not be obvious. This is a further reason why the inner side of the antecubital fossa should not be used for the injection of thiopentone unless the veins are easily visible.

In contrast with the above, the radial and ulnar nerves are not so accessible to damage.

In the antecubital fossa the radial nerve lies deep in the intermuscular furrow which is bound on the medial side by brachialis, on the lateral side by brachioradialis and below by the extensor carpi radialis longus. Its course in the forearm is likewise deep.

The ulnar nerve at the elbow lies in a groove on the back of the medial epicondyle and it enters the forearm between the two heads of flexor carpi ulnaris. In the antecubital fossa it lies on the posterior and oblique parts of the medial ligament of the elbow joint.

Intense shooting pain is the first symptom which is likely to follow the injection of thiopentone into a peripheral nerve. Sudden flexion of the wrist and thumb may occur when the median nerve is affected. Anatomical considerations show how the distribution of pain from the various nerves differs from that following intra arterial injection, and also demonstrates the ease with which the symptoms of this latter condition can be simulated by damage to the median nerve. A delay in the loss of consciousness may occur due to part of the solution entering the vein and the remainder being deposited into or around the nerve. Pain shooting down the forearm is not likely to be confused with that of intra-arterial injection.

The immediate treatment recommended for the injection of an irritant, like thiopentone, into or around a peripheral nerve is to leave the needle in position and inject 0 5 per cent. procaine, with hyaluronidase. This will dilute and disperse the thiopentone and help to neutralise its alkalinity Where the needle has been moved, either by accident or intentionally a generous infiltration should be carried out with the above solution around the site of injection. The spread of the local analgesic above the site of damage to the nerve will ease the intense pain.

The ultimate result of this accident will depend on the volume and concentration of thiopentone injected and the exact location of the needle tip As soon as the immediate symptoms subside and a definite diagnosis is made, an expert on peripheral nerve

lesions should be consulted The diagnosis can be made from the occurrence of sensory loss or muscle paralysis, but the former may be preceded by hyperaesthesia in the affected area for a few days Such measures as exploration of the site or damage with excision of scar tissue, splinting or muscle exercises may eventually be advocated.

GENERAL EFFECTS

Most of the hazards associated with the general effects thiopentone on the various systems are the result of overdosag This can be due to the administration of a greater than average dose (particularly if injected quickly) to a normal person o administration of a normal dose to a susceptible subject. Thi difference is of more than academic interest since fit patients are better able to stand the effects of overdosage, and recovery often takes place quickly without any intensive treatment. On the other hand, a prolonged period of depression may result from over dosage of thiopentone in poor risk patients The various pathological states which induce sensitivity to thiopentone have been discussed fully in the previous two chapters.

Failure to appreciate the limitations of thiopentone is probably the most common cause of overdosage. Such circumstances include its use as a sole narcotic for procedures lasting more than a few minutes and attempts to produce prolonged quiescence of laryngeal reflexes or muscular relaxation with the drug It has already been stressed that the cardiovascular system of patients who are resistant to the narcotic effects of thiopentone may not be able to stand the large doses which are necessary to produce anaesthesia. Accidental overdosage can result if the drug is temporarily trapped in the vein by an inadequately released tourniquet, a tight bandage, tight clothing or by the posture of the patient.

It will be appreciated from the classification of the mishaps due to the immediate general effects of thiopentone (p 194) that there is much overlap between its action on the cardiovascular and respiratory systems, and some of its actions on the former are secondary to hypoxaemia resulting from its effect on respiration. The discussion on the mortality rate associated with the use of thiopentone has shown that a fatal outcome is most frequently the

result of the direct toxic effect of the drug on the myocardium However, to avoid repetition, the actions on respiration will be discussed first.

Momentary apnoea is the recognised response to the injection of a full induction dose of thiopentone. However, when it persists for more than half a minute in fit subjects or for more than a few seconds in poor risk patients it must be treated by artificial respiration with oxygen or with nitrous oxide/oxygen The use of analeptics is not recommended in deep anaesthesia. Artificial ventilation can easily produce hypocarbia, and carbon dioxide may be added intermittently to the mixture in concentrations not exceeding 5 per cent. of the total gases. Carbon dioxide *per se* plays no part in the treatment of apnoea or severe respiratory depression due to thiopentone, since the sensitivity of the respiratory centre to this metabolite is abolished completely in severe overdosage with the drug Rhythmic overdistension of the lungs alone can prolong apnoea. Where spontaneous respiration is being maintained by the stimulus of hypoxia on the carotid body, (as during the intermittent or continuous administration of thiopentone as sole narcotic) the inhalation of oxygen or oxygen rich nitrous oxide/oxygen mixtures may remove this stimulus and result in apnoea.

The return of spontaneous respiration does not imply that the tidal volume has returned to normal and respiration may require assistance for some time. Nor is absence of cyanosis a reliable guide to the sufficiency of respiration for while the patient may be reasonably well oxygenated hypercarbia may be developing Since the shift of the stimulus to respiration from carbon dioxide to hypoxia is accompanied by a reduction in tidal volume, it is recommended that supplementary inhalation agents should invariably contain more than the atmospheric concentration of oxygen. This will help to eliminate undetected respiratory depression during deep thiopentone narcosis.

Respiratory depression may appear for the first time at the end of operation. This is most likely to be due to conclusion of surgical stimuli and a lapse of the patient into a clinically deeper level of narcosis. It may also result from the reduction of alveolar carbon dioxide tension to normal in cases where there has been an increase in dead space, incomplete carbon dioxide absorption by soda lime in closed circuit anaesthesia, or insufficient total flow of gases in

There is always an exciting cause, which is most frequently an endotracheal tube. It is most likely to occur in the same types of patient who are prone to laryngeal spasm. It may not be feasible or desirable to remove the tube. Bronchospasm can be relieved by deepening the anaesthesia with more thiopentone, by administering a bronchodilator drug such as aminophylline or pethidine, or by the use of suxamethonium. Where there is a persistence of a minor degree of bronchospasm during anaesthesia it can usually be relieved by the intravenous administration of atropine or pethidine. Before carrying out any of the above procedures one must ascertain that resistance to respiration is in fact due to bronchospasm and not due to such things as a kinked endotracheal tube, obstruction of the tube by a foreign body or a cuff which has spread over its lower end.

Respiratory obstruction due to aspiration of stomach contents has already been dealt with in detail. Blood, pus or foreign bodies may be aspirated during operations on the upper respiratory tract, and can cause varying degrees of respiratory obstruction. Prophylaxis is of first importance in these operations, as it is in those patients who are prone to aspirate gastric contents during induction. A cuffed endotracheal tube should be passed as a routine before the operation is commenced or the head should be postured so that blood and pus can be aspirated from the pharynx. The technique of keeping an intact cough reflex present, such as is frequently used during tonsillectomy should not be practised with thiopentone alone, because of the dangers of laryngeal spasm. Where there is any suspicion of aspirated foreign bodies or fluid, tracheal suction must be carried out as soon as feasible. If there has been a delay in suction, or where solid material, such as teeth, have been aspirated, bronchoscopy must be performed at the completion of the operation.

The proverb prevention is better than cure is nowhere more applicable than to the effects of thiopentone on the cardiovascular system. Conditions where sensitivity can be expected to occur have already been mentioned elsewhere and the precautions advocated during the use of thiopentone in such patients have been described.

There is usually some degree of hypotension following the injection of thiopentone, but this is often of no importance. Cardiovascular collapse from overdosage should be treated by

putting the patient in the Trendelenburg position Equally important is the immediate correction of hypoxia from the concurrent respiratory depression. Where these measures produce no improvement, a *l* noradrenaline infusion should be set up Ouabain or digoxin may be given intravenously, and if there is any evidence of pulmonary oedema, this should be treated with aminophylline and tracheal suction.

Falls in blood pressure which occur late after the administration of thiopentone are secondary either to the action of hypoxia or hypercarbia, ineffective treatment of early hypotension affecting the coronary blood flow, or the result of blood loss during operation or the surgical manipulations. Hypoxia during thiopentone anaesthesia results in a gradual depression of the blood pressure, and treatment will be ineffective if the cause is not removed. The blood pressure rise which normally follows hypercarbia is prevented by doses of thiopentone which depress the respiration (Fig 22). A sudden withdrawal of carbon dioxide may result in severe hypotension similar to that described by Dripps (1947) after the use of cyclopropane. This should be treated on the same lines as described above.

The treatment of hypotension resulting from blood loss has been discussed in the section on shock. Falls in blood pressure due to the manipulations of the surgeon are similar to vaso-vagal attacks and can occur during too light anaesthesia. Recovery usually takes place spontaneously but it can be hastened by the use of a vaso-constrictor drug

It must be remembered that delay in the return of consciousness after thiopentone can be due to factors other than an overdose of the drug This latter occurs most commonly when a large dose is administered to a suceptible person, especially where there is some interference with diffusion and detoxication of the drug The suggested treatment for this has already been fully discussed on page 173

A period of prolonged hypoxia during or after the administration can delay the return of consciousness, the prolongation of coma varying with the degree and duration of the hypoxic episode. This latter may have been due to profound hypotension or respiratory insufficiency, and steps should be taken to restore the blood pressure or ensure adequate oxygenation and carbon dioxide removal. It has been suggested by Sadove, Wyant and Gittelson

(1953) that cerebral oedema is partly responsible for prolonging the coma in such cases. Repeated injections of 50 to 100 ml. of 50 per cent. sucrose or dextrose, concentrated serum albumen, or double or quadruple concentrated plasma, should be given intravenously at frequent intervals. This can be combined with other measures designed to produce dehydration, such as magnesium sulphate enemata. The general treatment of these patients should be on the same lines as for coma due to thiopentone. Analeptics should not be given, and special care should be taken with respect to tracheo-bronchial toilet as coma may persist for several days. The diagnosis of whether coma is due purely to an overdose of barbiturates or is prolonged by the effects of cerebral hypoxia rests mainly with the history of events during the anaesthetic and the presence of papilloedema.

Occasionally one encounters prolonged narcosis which is in no way associated with the anaesthetic but which may be precipitated by the surgical procedures. One such case is recorded by Geddes (1952)

A male aged 31 had cerebral angiography performed as a diagnostic procedure for hemiparesis of slow onset. Anaesthesia was with thiopentone/gallamine triethiodide/N_2O/O_2/trichlorethylene, the exact doses given not being stated. Atropine gr $\frac{1}{100}$ (0·65 mg.) and followed by neostigmine 2·5 mg. were administered before leaving the X-ray department, and restored respiration to normal.

He was still unconscious 6 hours after return to the ward. Blood pressure was 130/100, pulse regular. 40 ml. of 50 per cent. glucose was given intravenously as an internal hydrocephalus was shown on the angiograms. A return to consciousness followed and no aggravation of the existing paresis was evident next day.

It must be appreciated that the apparent return of full consciousness immediately after thiopentone or any barbiturate or thiobarbiturate does not imply that mental faculties have completely returned to normal. Von Felsinger, Lasagna and Beecher (1953) have demonstrated a significant impairment of visual perception, attention and arithmetic performance for between 5 and 8½ hours after the oral administration of 100 mg. pentobarbitone. On recovery from sleep after taking the drug, 85 per cent. of subjects complained of fatigue or grogginess as compared with 50 per cent. of those receiving a placebo. The latter effects are frequently observed on recovering from thiopentone, and the probability of undetected mental impairment is such that, under

no circumstances, should patients who have recently received the drug be allowed to leave hospital unaccompanied. The dangers of this practice are illustrated by the following case report.

A fit young man was admitted to hospital as a 'day case" for oesophagoscopy which was carried out under thiopentone and a relaxant. It was arranged that a relative should take the patient home by car on the evening of the operation. About 2 to 3 hours after return of consciousness the patient seemed quite normal and he was told to dress as he would soon be leaving hospital. Without waiting for his escort, the patient set off for home. His journey necessitated changing buses, and this he negotiated satisfactorily He alighted at the correct bus stop but was unable to find his home, and he was found 1 hour later wandering around in a dazed condition. This occurred about 8 hours after the anaesthetic and 4 to 5 hours after the return of consciousness. On enquiring later, neither the ward nurse nor one of the bus conductors (who knew the patient personally) recalled noticing anything abnormal in his behaviour at the time.

The following case-report, which concerns hexobarbitone, is much more dramatic and resulted in a claim for damages being brought against a dental surgeon (*Lancet* 1949)

A dental surgeon intended to extract 7 teeth in a patient for whom nitrous oxide was deemed unsuitable. The patient was told that he was to be given an intravenous anaesthetic and that he would probably be very drowsy for at least an hour after the extractions The patient's own doctor injected 550 mg of soluble hexobarbitone the teeth were extracted, and the patient was carried to a couch in the surgery Nikethamide was given to accelerate recovery About a quarter of an hour later the dental surgeon went to lunch, instructing the nurse to report to him if the patient began to come round. Within a few minutes the nurse reported that the patient was fingering his shirt at the neck. Returning immediately the dental surgeon found the patient apparently asleep so he returned to lunch.

"Twenty minutes later the nurse, who had kept looking into the surgery found that the patient had gone. It transpired that he had driven off in his car and, when stopped by traffic lights, had been addressed by a policeman who, suspecting that something was amiss, kept him in conversation. The constable learned that the patient had just had teeth extracted he offered to drive the patient home, but the offer was refused. On reaching his garage about a mile further on, the patient collided with a wall and a petrol pump and on getting out of the car he collapsed and was helped upstairs he remained unconscious for a further 4 to 5 hours. The dental surgeon s claim for the amount of his fee was met by a counter claim for damage to the car arising through negligence in that, *inter alia*, the nurse had not prevented the patient from leaving the surgery while still under the influence of the drug "

The case was defended successfully by the Medical Protection Society on the grounds that the patient had been warned of possible side-effects and he had made an error of judgment in going by car to the operation without arranging for someone else to drive him home. Moreover it was argued that on the way home the patient had so far recovered as to be capable of making a sound independent judgment of his movements and of whether he should accept the constable's offer to drive him home. His decision to drive himself home without the dentist's permission constituted a *novus actus interveniens* which broke the claim for causation of the damage.

In view of the work of von Felsinger *et al* (1953) it is improbable that a patient is capable of making a sound independent judgment as stated above, so soon after a barbiturate. A patient who on recovery from thiopentone, finds he is not allowed to leave hospital because no escort has been arranged for the journey home may decide to sign a form stating that he is leaving at his own risk. The value of such a statement as defence against any claims for damages which result from a mishap on leaving the hospital is very doubtful since, at the time when the patient makes the decision to leave on his own, he is not in full control of his powers of judgment.

All out patients who are to receive thiopentone must have the hazards explained to them beforehand and an escort for the journey home must be insisted upon. Unless arrangements are made for this escort or the patient is willing to spend the night in hospital, thiopentone should not be given.

The question arises as to how soon after thiopentone the patient can be considered to have returned to normal. This depends on many factors especially the dose of thiopentone given, the duration and nature of the operation and the general condition of the person. Considering the alertness of patients on the morning after operation, when thiopentone has been given on the previous afternoon or evening it seems a wise rule to insist on a period of normal sleep after recovery from the anaesthetic. This only applies if no sedative or potent analgesic drug has been given to facilitate the onset of sleep

Post-operative restlessness after thiopentone is seen most commonly when the drug has been given by the rectal route to children, especially for operations which are likely to be followed

by severe pain such as tonsillectomy This is another manifestation of the lack of analgesic properties of the drug and the condition is analagous to the delirium of second-stage anaesthesia with ether The treatment is to administer an analgesic drug such as pethidine or levorphan and to withhold all sedatives, as the latter would delay the return of consciousness and prolong the delirium The slower rate of recovery is the reason why post-operative restlessness is more commonly seen after basal narcosis with medium acting barbiturates, such as pentobarbitone and quinalbarbitone, than after thiopentone.

DELAYED TOXIC EFFECTS

It is not proposed to discuss these in detail, as they have been referred to elsewhere. The effect of large doses of thiopentone on liver function is shown in Fig 25 and thus leaves no doubt as to the dangers of its use in patients who already have hepatic damage. In the following case report the occurrence of the 'hepato-renal" syndrome may have been due in part to the large amount of thiopentone administered during anaesthesia.

A woman, aged 67 weight 140 lb (63 kg), had a history of jaundice for more than 3 months. The liver was enlarged and the gall bladder palpable. Liver function tests revealed obstructive jaundice (direct Van den Bergh reaction serum alkaline phosphatase 35 Armstrong King units) The blood urea was 45 mg per cent. and Hb 11·8 gm. per cent. Operation was a palliative cholecystenterostomy for a tumour of the head of the pancreas, operating time being 105 minutes. Anaesthesia was with thiopentone (950 mg)/d tubocurarine chloride/cyclopropane/oxygen and consciousness was not regained until 6 hours after return to the ward. Liver biopsy taken at operation, revealed dilatation of bile ducts and biliary cirrhosis.

The patient passed very little urine on the day after operation and 5 per cent. dextrose was given. Anuria occurred on the second post operative day and was successfully treated with intravenous procaine. On recovery from the anuria large numbers of bile-stained casts were passed, some of which appeared to reproduce the tubular pattern of nephrone casts seen in the injection studies of kidneys.

The blood urea continued to rise and was 85 mg per cent. on the fifth post-operative day and 105 mg per cent. 3 days later On the ninth day after operation there was copious blood-stained vomitus and the patient lapsed into coma and died.

The history between the end of the operation and the decease is typical of the hepato-renal syndrome. The exact aetiology of

this is not known, but it has been suggested that hepatic dysfunction becomes progressively more pronounced when the added strain of surgery is put upon it. In this case there was the additional strain of detoxicating an overdose of thiopentone.

The late sequelae of hypoxia vary from slight mental impairment to prolonged coma with decerebrate rigidity. Some improvement may be expected with the former but the prognosis is poor if consciousness has not returned within 2 to 3 days.

The dangers of an acute exacerbation of the disease following the administration of thiopentone to patients with porphyria or Addison's disease have been adequately stressed elsewhere. The treatment for these is the same as for attacks induced by any other means.

HAZARDS NOT DIRECTLY DUE TO THIOPENTONE

Damage to the brachial plexus, musculo-spinal and ulnar nerves have all been reported following anaesthesia. In most cases an arm has been abducted, and secured to an arm-splint, for transfusion purposes or for intermittent injection of the anaesthetic. Radial and ulnar palsies are caused by the direct pressure of the splint on the nerves and can be prevented by proper padding of the splint. The situation is not so simple in lesions involving the brachial plexus, and although these are not a hazard of thiopentone *per se* they will be briefly reviewed.

The anatomy of the brachial plexus arising as it does from 5, 6, 7 and 8 cervical and first thoracic roots, with small contributions from the root above and below is important in understanding the mechanism of the injuries. The nerves pass downwards and laterally on the scalenus medius enveloped in the cervical prevertebral fascia which is attached to the transverse processes of the cervical vertebrae, and thus anchored proximally. Distally they are equally firmly fixed by the axillary fascia. In their course in the axilla they pass deep to the tendon of pectoralis minor and are in close relationship with the head of the humerus. The lower trunk is formed very close to the upper surface of the first rib and communications from the first and second thoracic roots arch over this rib. Post fixation of the plexus or the presence of a cervical rib will cause an increase in the fibres taking this route.

From the above it will be appreciated that depression of the shoulder-girdle will lengthen the distance that the nerves have to take in the neck and result in stretching. Similarly abduction of the arm puts a tension on them, which is increased with external

rotation at the shoulder joint, extension of the elbow and supination of the forearm If to this is added fixation of the shoulder, so that it cannot rotate when the arm is abducted, the humerus pivots on the acromion process and the head of the humerus is forced into the axilla, and bulges the lateral wall. This adds to the stretching of the nerves. In addition, if the arm is abducted as described above but on a plane posterior to that of the shoulder girdle (as happens when the gall bladder bridge is used, or where an improperly padded arm is placed under the mattress), the nerves and vessels in the axilla are also tensely arched over the tendon of pectoralis minor

When the Trendelenburg position is used and shoulder rests are fitted to take the weight of the patient, there is a distraction force operating on those structures passing between the shoulder-girdle and the trunk. In the conscious state this is taken on the muscles, until they become fatigued If the muscles cannot take the strain, either from the use of a relaxant, from deep anaesthesia or from fatigue, then this must be borne by other structures passing from the neck to the shoulder-girdle The brachial plexus is relatively inelastic and fixed above and below and hence it is subject to severe stretching in the circumstances described.

This stretching is widely accepted as the causation of post operative lesions of the brachial plexus. Most cases described in the recent literature have been in the Trendelenburg position with the use of shoulder-rests, the arm has been abducted and a muscle relaxant has been used (Ewing, 1950) Kilock (1950) has described brachial palsies after abduction or hyperextension and external rotation of the arm after operations in which the gall bladder bridge was raised and a muscle relaxant given. Rollason (1950) has recorded its occurrence after the use of thialbarbitone/nitrous oxide/oxygen without a relaxant when the arm was hyper-abducted and externally rotated. Pressure on the plexus by the shoulder rests has also been incriminated and in some cases would appear to be the cause, when these have not been properly padded and placed too far medially, perhaps at different levels on the two sides. Nipping of the nerves between the clavicle, the transverse process of the lower cervical vertebrae and the first rib has also been suggested as a possible cause.

The reported lesions have mostly involved motor nerves with little sensory loss, usually an Erb-type paralysis involving the

upper trunk of the brachial plexus. The prognosis is good although recovery may take a year or more, and there is frequently a residual aching and tenderness of the plexus and the muscles affected. Sensory loss recovers more rapidly than the motor weakness. Active treatment can only consist of rest and such physiotherapy as will prevent stretching of the paralysed muscles and relaxation of the affected nerves.

Prophylaxis is important, for as has been recently remarked (*Lancet* 1950) despite the old saying that a change is as good as a rest, few patients really relish exchanging one disorder for another The Trendelenburg position should be adopted as little as possible. If it is to be used shoulder pads should be well padded and placed over the tip of the acromion process and the arm should not be abducted. Even when not in the Trendelenburg position, the arm should never be abducted to more than 90 degrees from the trunk, and external rotation is not permissible. When the gall-bladder bridge is raised, the abducted arm should be supported and not allowed to remain in a position posterior to the shoulder-girdle. Arm-boards should be properly padded so that the shoulder is not at a higher level than the arm. The head should not be turned away from an abducted arm. It should be remembered that alternative means have been described for fixing the patient on the table in the Trendelenburg position other than the use of shoulder rests. The most valuable of these appear to be the pelvic rests which grip the iliac crest and the use of a rough rubber mattress which holds the patient by friction with the skin.

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THE THERAPEUTIC USES OF THIOPENTONE

THESE are mostly dependent on the anti-convulsant properties of thiopentone, although some use is made of its narcotic action with the rapid onset of anaesthesia and prompt recovery after small doses

AS AN ANTI-CONVULSANT

Eclampsia. Thiopentone is widely used for the control of fits in eclampsia and has had some vogue as an agent for their prophylaxis in women suffering from severe toxaemia. This latter use was popularised by O Donel Browne (1950) who used a solution consisting of 3 g thiopentone to 1 litre 5 to 10 per cent. dextrose, with additional injections of a 5 per cent. solution into the drip as required. At first morphine was used in addition to thiopentone, but was abandoned because of respiratory depression. In a series of 18 patients who had this treatment the incidence of fits was 22 per cent. with a mortality of 5·5 per cent. as compared with 55 per cent. incidence of fits and 20 per cent. mortality in a previous series of comparable patients treated with magnesium sulphate and glucose. In 2 of the above cases who had fits the dosage was inadequate, and in a further 2 it was stopped prematurely The average dose of thiopentone administered by O Donel Browne was 4·9 g given over 25 hours (range 1·75 g in 10½ hours to 7·9 g in 35 hours) and recovery of consciousness took 6 to 12 hours.

Menon (1953) has reported the results of treating 75 patients with a modification of the above technique 0·3 per cent. thiopentone was administered in 20 per cent. dextrose for 24 hours (maximum dose 5 g thiopentone) followed by 20 per cent. dextrose alone for a further 24 to 48 hours. Oxygen was administered throughout, and increment doses of 100 mg thiopentone were injected into the drip as required. Once the treatment was started, only 9·5 per cent. of patients had a recurrence of fits. However the overall mortality was 16 per cent. of which one

half was due to acute cardiac failure. A pulse rate of 140 or more per minute, falling blood pressure and rapid respirations were bad prognostic signs. Reviewing the treatment, Menon remarks that "while thiopentone is the best method of controlling fits, it has not helped to bring down the maternal mortality" He concludes, 'I have come to the conclusion that thiopentone is not very harmless to the eclamptic . . . have lost too many patients for no other obvious cause than acute cardiac failure setting in during the treatment.'

As an emergency measure to control eclamptic fits the injection of thiopentone is most practical and effective. Macintosh (1952) considers that not only does it raise the convulsive threshold but it relaxes vascular spasm, which is a potent factor in initiating and maintaining a convulsion. There may be considerable technical difficulty in introducing the needle into the vein during the fit and, while exercising reasonable caution, an adequate injection must be made once the vessel is entered. A suitable initial dose is 250 mg., and depending on the response, this may have to be increased to 300 mg. Once convulsions have been controlled, an infusion of 0·3 per cent. thiopentone may be started but considering the general condition of these patients it seems more logical to administer paraldehyde per rectum since it has much less depressant action on respiration and circulation than large doses of thiopentone.

Convulsive movements of the limbs and the urgency of the injection make it difficult to observe the usual precautions for avoiding intra arterial injection. For this reason the strength of the thiopentone solution should not exceed 2·5 per cent. Extra venous injection is also more likely to occur in these circumstances, and while the dangers of this sort are decreased by the use of dilute solutions, some workers prefer *hexobarbitone* because of its less irritant effects on the tissues. It is hardly necessary to stress that respiratory depression should be vigorously combated after the use of thiobarbiturates to control the convulsions of eclampsia. Occasionally one may encounter an eclamptic being treated with the methonium compounds or continuous spinal block, and in these the dosage of thiopentone should be kept to a minimum and the injection given slowly to reduce the effects of the drug on blood pressure.

Anaesthetic Convulsions. *A Local Analgesia* The treat

ment is essentially the same as for eclamptic fits However in the latter one aims at having the patient depressed by drugs for some time to prevent recurrence of the convulsions, while after an over dose of a local analgesic it is desirable to have the patient conscious as soon as possible. Once the spasms have been controlled, no further drug should be injected until there is a sign of the return of convulsions [1] With a slight overdose of a rapidly metabolised drug such as procaine, one dose of thiopentone may be sufficient, but with the longer acting agents sufficient of the analgesic may remain in the blood stream to cause further convulsions as the cortical depression wears off. Very small increment doses of thiopentone will suffice for their control, and the dosage can be reduced by the use of muscle relaxants which block the peripheral mechanisms for convulsions. Endotracheal intubation is advised after the use of relaxants and respiration should be assisted until their effects wear off

B General Anaesthesia This refers to convulsions from a variety of causes which occur during general anaesthesia and which are often called ether convulsions Wood Smith (1949) states that the mortality from anaesthetic convulsions has been reduced from 19·3 per cent. to 11·5 per cent. since the introduction of the rapidly acting thiobarbiturates. In these cases thiopentone is used only for the immediate control of convulsions, and steps should be taken to remove the cause. Among the aetiological factors which are amenable to treatment are hyperpyrexia, dehydration hypoxia, carbon dioxide excess or deficiency toxaemia and cerebral congestion. Since the patients are often already deeply anaesthetised, very little thiopentone should be given since apnoea and hypotension can easily occur It is frequently stated that anaesthetic convulsions start in the face, and although Williams and Sweet (1944) have shown that this is not always the case, twitching of the face should be taken as an indication for the immediate injection of thiopentone. Once the convulsions have become generalised there may be considerable difficulty with venipuncture, and the precautions outlined in the treatment of eclampsia should be observed.

Children are particularly prone to convulsions during anaes-

[1] In this connection it is recommended that one should always have some thiopentone prepared in a syringe when using local analgesics, particularly with the topical application of cocaine or amethocaine

thesia. This may be due to the instability of their nervous system their liability to hyperpyrexia or their tendency to hyperventilate The widespread use of ether in paediatric anaesthesia may also be a contributory factor The difficulty of venipuncture in very young children renders the immediate control of convulsions difficult, and unless the administrator is experienced in this respect less time will be wasted by the immediate rectal administration of thiopentone. More often than not the exact weight of the child will not be known, and even if such information is available one can only guess what percentage of the basal narcotic dose will be required to control the convulsion Below are given the average weights for different ages in male children and the amount of thiopentone required to produce basal narcosis in the unanaesthetised state. It is suggested that half this dose should be given without delay

Age	*Average Weight of Male*	*Thiopentone required to produce Basal Narcosis*		*Dose to control Convulsion* (ml. 2·5%)	
				Male	*Female*
	lb.	mg	ml. 2 5%		
6 mths.	16	400	16	8	7
1 year	24	600	24	12	11
2 years	28	700	28	14	13
3 years	32	800	32	16	15
4 years	36	900	36	18	17
5 years	40	1000	40	20	19
6 years	44	1100	44	22	21

These values are only approximate and are simplified so as to be easily remembered. The dose should be reduced for children who are obviously below the average weight for their age. The quickest method of giving the thiopentone is to pass a urethral catheter into the rectum, clamp the open end as near the anus as practicable and inject the ordinary solution prepared for anaesthesia into the catheter with an ordinary syringe. A further injection of saline or water should be made to wash the contents of the catheter into the rectum. Oxygen should be administered while the thiopentone is taking effect and artificial respiration will usually be required once the convulsion has been controlled.

Convulsions from Other Causes. Thiopentone has been

used for the immediate control of the convulsions of tetanus. Because of severe toxaemia and the importance of obtaining a clear airway it is frequently necessary to combine the narcotic with a rapidly acting relaxant. As a prolonged method of treatment of tetanus, muscle relaxants are recommended, a light level of narcosis being maintained with nitrous oxide/oxygen, a medium acting barbiturate or paraldehyde. Convulsions from other causes, such as epilepsy can be rapidly controlled by thiopentone, provided there is no contraindication to its use.

AS A NARCOTIC

Psychiatry Barbiturates were introduced as therapeutic agents in the field of psychotherapy by Horsley in 1936. During the pre-comatose state or during emergence from unconsciousness, inhibitions are abolished or lessened, and this phase can be prolonged by the slow injection of the drugs. As in hypnosis, there is some dissociation and the subject is more than ordinarily suggestible. In this field amylobarbitone and pentobarbitone are more popular than thiopentone. The more rapid onset of action of the latter may make it difficult to establish communication with the patient at first.

Narcoanalysis or Narcosynthesis with barbiturates has been used as an aid in the diagnosis of psychoses, both in depressive states and catatonic schizophrenics and in the diagnosis and treatment of neuroses. In the acute neuroses of war it has been found valuable in treating functional amnesia and conversion symptoms of recent and abrupt onset, and for the abreaction of emotionally changing experiences. Its chief usefulness seems to be in the rapid recovery of memory in psychogenic amnesia and in discriminating between hysterical and organic disorders.

Criminology Lhermitte (1951) favours the use of thiopentone in criminal cases for the detection of malingering ('narco-diagnosis') but not for obtaining information about the guilt of the accused ('narcoanalysis'). If used in criminal cases, ethical problems are raised, for an accused may be placed at a disadvantage if it were revealed at his trial that he had refused to submit to narcoanalysis. In 1953 for the first time in Britain, statements made under the influence of thiopentone, by a young man accused of murder were put forward by a psychiatrist who

was called as an expert witness for the defence This medical evidence was accepted by the Court, and the jury after deliberating for two hours found the accused guilty but insane (*Lancet* 1953)

Alcoholism. Lemere and O Hollaren (1950) and Lemere, Berard and O Hollaren (1952) have reported the use of thiopentone, combined with psychotherapy in the treatment of chronic alcoholism It has also proved of value as a means of providing relaxation and relief from the emotional tension from which the alcoholic so often suffers From 300 mg to 1 g of thiopentone is given during each treatment, which takes 15 to 60 minutes. During the first part of the treatment the level of anaesthesia is light enough for the patient to be questioned concerning his problems, and he is later put under deeper anaesthesia so that he may sleep as long as possible. Five to eight injections of thiopentone are given in the first series of treatments which lasts from one to two weeks depending on whether the thiopentone is given alone or on alternating days with aversion treatments. Following this the patient returns once a week for a few weeks then once every two or three weeks and finally once every month or two, depending on the case. The average number of injections of thiopentone per person has been fifteen Over five years these workers have administered thiopentone 15 504 times to 1027 patients and have found that it has been of great assistance in helping many people to learn to live without alcohol

The rapid onset of narcosis with thiopentone has led to it being advocated for the sedation of drunken disorderly subjects. Because of a full stomach, the difficulty of venipuncture and the synergistic action of alcohol and barbiturates this treatment is not without danger It has been suggested that, if venipuncture is possible, injections of multiple vitamins or vitamin B6 should be given. This multiple vitamin treatment is discussed in more detail on page 271

Hysteria. The successful treatment of hysterical paralysis with thiopentone and psychotherapy has been reported by Somerfield and Tovell (1941) Light anaesthesia was induced with thiopentone and the limb stimulated until the patient complained. The author has heard of its successful use in the treatment of hyperemesis associated with pseudocyesis, and of the inability to write which the patient wrongly attributed to poliomyelitis.

Alvarez (1947) has described a syndrome of intermittent abdominal distension due to "neurosis of the abdominal wall. Of his 74 cases, the majority were females who were neurotic and frequently complained of migraine or allergic phenomena. Symptoms commonly began in youth and the onset could be traced to an unhappy marriage, divorce or some other emotional upset. Attacks increased in frequency with time until some patients had almost continuous distension which was associated with pain of such severity that a few became addicted to morphine.

Gaseous distension was excluded as a cause for the syndrome, but spasm of the back and upper abdominal muscles, together with the assumption of a lordotic posture appeared to throw the adbominal contents forward and down into the pelvis. Lying supine with the knees drawn up or on the side with the thighs flexed on the abdomen (as for lumbar puncture) overcame the lordosis and the abdomen became flat and soft.

Among the various therapeutic measures which have been found to produce temporary symptomatic relief were the injection of morphine, splanchnic block, onset of vomiting or induction of anaesthesia. Since it may be necessary to relieve the symptoms repeatedly until the psychological background to the disease is corrected, thiopentone seems eminently suited for this purpose, provided none of the recognised contraindications to its use are present.

MISCELLANEOUS THERAPEUTIC USES

Soon after its introduction, Allen, Lundy and Adson (1936) suggested that thiopentone be given to determine the blood-pressure fall expected from bilateral thoraco-lumbar sympathectomy. Amylobarbitone in three divided doses of 200 mg given at hourly or two-hourly intervals is preferred to thiopentone, because of the more constant level of narcosis which it induces. Opinions differ as to the value of any barbiturate as a prognostic test of the benefit of sympathectomy in hypertension and many other factors must be taken into consideration before deciding that a patient is suitable for such an operation.

Hunter (1947) has shown that the time interval 15.5 to 16.0 seconds between the administration and the onset of sleep with thiopentone (150 mg.) and hexobarbitone (300 mg.) is an indication of the arm brain circulation time, and approximates to the arm-tongue and arm-carotid sinus circulation times determined by other methods. Thiobarbiturates offer a simple method of comparing the circulation rate in various pathological conditions,

provided there are no contraindications to their use in the above dosage.

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Chapter IX

THE ADMINISTRATION OF THIOPENTONE

This chapter could equally well be called Thiopentone and the occasional Anaesthetist. The intention is to summarise the most important data from the clinical point of view and present a simplified picture of the uses and limitations of the drug. As most of what has to be discussed has been referred to in greater detail elsewhere, for the sake of clarity references which appear elsewhere in the book will not be included.

Thiopentone is an unstable sulphur-containing narcotic, the sodium salt of which is freely soluble in water. The latter is inactive by mouth and too irritant for intramuscular or subcutaneous injection. It is usually prepared for use in a 2·0 to 5·0 per cent. aqueous solution, but occasionally a 0·3 per cent. infusion is preferred. Its intravenous administration leads to reversible depression of the central nervous system.

PHARMACOLOGY

The terms short-acting or ultra-short acting by which thiopentone and similar drugs are frequently referred to, are misleading. Thiopentone is rapid acting, the onset of narcosis depending on the arm brain circulation time. This is about 15 seconds in healthy adult subjects, but is increased in states of shock and cardiac inefficiency. Failure to appreciate this can easily lead to an overdose being administered. Far from being short acting the effect of a single injection of thiopentone can be demonstrated for up to 30 hours after injection in man.

The level of the drug in the blood stream is almost immediately reflected by changes in the cerebrospinal fluid and brain content, and the depth of consciousness is related, among other factors, to the plasma content of thiopentone. Recovery after a small induction dose (200 to 300 mg for an adult) is due to rapid removal of the drug from the blood stream and its location in such non nervous tissues as the liver and kidney. The plasma level falls rapidly and the patient wakens. While the liver and kidneys

reach equilibrium with the plasma within 1 minute of injection the muscles continue to absorb the drug for about 15 minutes and help in the recovery of consciousness, if this has not been brought about by the earlier redistribution. Fairly frequent increments will be required if it is intended to maintain anaesthesia for a period up to 15 minutes with thiopentone alone.

With the administration of large doses or with prolonged administration, the early diffusion may not immediately reduce the plasma level below that at which recovery occurs. Fat shows special affinity for thiopentone, but presumably because of its poor blood supply does not take up the drug with the same rapidity as most other tissues. It continues to withdraw the drug from the plasma for about 2½ hours after injection, and as its final content of thiopentone is greater than that of any other tissue, it plays an important part in bringing about the recovery of consciousness after large doses. Detoxication, which mainly occurs in the liver, is a slow process and only 10 to 15 per cent. of the drug in the body is broken down per hour. It does not play an important part in the recovery after small doses, and because of its slowness a cumulative effect will be observed when a repeat dose of thiopentone is given within 30 hours of a previous dose.

The plasma level of thiopentone at which consciousness returns varies from patient to patient and also varies at different times in the same patient. It is related to the peak concentration of the drug in the blood stream and hence to the maximum concentration attained in the brain. With rapid injection of thiopentone, producing a high initial plasma level, recovery is more rapid than if the same dose were given slowly. The longer anaesthesia continues, the higher will be the plasma level of thiopentone at which the various signs of recovery become apparent.

Diffusion of thiopentone will be impaired by any factor which decreases the blood supply to the tissues concerned. The most common of these is the clinical state generally referred to as shock. Not only will the ultimate recovery be delayed if a 'normal' dose is given to patients in this condition, but a deeper level of narcosis will result from the induction dose.

While thiopentone is one of the best narcotics known, it has virtually no analgesic properties. Depression of the brain follows the same pattern as occurs with any other anaesthetic, but the

clinical depth of anaesthesia often bears little relationship to the degree of cerebral depression. One of the main reasons why the signs and stages of anaesthesia with ether follow so consistent a pattern is that this irritant vapour acts as a constant stimulus to which the patient will respond in a constant manner at the same depth of depression. No such stimulus is present with thiopentone and the clinical depth of anaestheasia is greatly dependent upon the intensity of stimulation. This stimulation can be reduced by premedication or intravenous supplementation with analgesic drugs The greater analgesic power and the curariform action of ether suppresses reflex activity at a lighter plane of narcosis than occurs with thiopentone. It may frequently be necessary to produce apnoea with thiopentone before reflex movement in response to painful stimuli is completely abolished, and for this reason it should never be given alone for other than extremely short operations Where it is possible, supplementations should be carried out with an analgesic drug the safest and most reliable being a non hypnotic mixture of nitrous oxide and oxygen. Thiopentone produces poor muscular relaxation and should not be used alone in abdominal and other operations during which prolonged relaxation is required.

After a brief stimulation, thiopentone depresses respiration until apnoea is reached at a depth of narcosis which is frequently insufficient to abolish reflex activity The sensitivity of the respiratory centre to carbon dioxide is markedly depressed, its stimulating action being completely abolished in deep anaesthesia. The laryngeal reflexes are relatively unaffected in light narcosis and closure of the glottis will readily occur in response to stimulation For this reason laryngeal spasm is more common after the use of intravenous anaesthesia than after most inhalation agents. However the drug itself does not cause laryngeal spasm. There is slight constriction of the bronchioles and bronchi during thiopentone narcosis.

Thiopentone has a direct depressant action on the myocardium, this being proportional to the concentration of the drug in contact with the heart. The effect of repeated doses on the myocardium is cumulative, and the unhealthy heart is more sensitive to the drug A fall in blood pressure usually follows the administration of thiopentone, and is partly due to the peripheral dilatation which occurs Its effect on the pulse rate is variable and is usually

secondary to its action on the blood pressure Thiopentone does not increase the irritability of the heart. Cardiac irregularities observed during its administration are thought to be secondary to hypercarbia or hypoxia resulting from respiratory depression

Thiopentone crosses the placental barrier in appreciable concentrations within five minutes of its administration In large doses it can cause prolonged impairment of liver function although its effect on blood sugar is negligible.

Thiopentone is almost completely metabolised in the body and only minimal amounts of the unchanged drug can be detected in the urine. Its metabolites, which possess no narcotic properties, are excreted in the urine and faeces.

USES

After this brief outline of the fate in the body and the most important actions of thiopentone it is advisable to consider the indications for its use. Adriani (1952) has admirably defined these as follows

(1) As an anaesthetic for brief surgical procedures.
(2) As a basal hypnotic to supplement nitrous oxide, ethylene other anaesthetics of low potency or in combination with analgesics.
(3) To relieve convulsive states produced by stimulant drugs or other causes.
(4) As a hypnotic in conjunction with regional anaesthesia (spinal nerve block, etc.)

The second indication listed above can be enlarged to include basal narcosis before the use of a powerful volatile or gaseous anaesthetic agent. This is probably the most common use of thiopentone in routine anaesthetic practice.

It is instructive to realise that Adriani refers to thiopentone as an anaesthetic and as a basal hypnotic In so far as the word Anaesthesia" as conceived by Oliver Wendell Holmes, refers to loss of sensation, thiopentone is a satisfactory anaesthetic. Today the more commonly accepted meaning of this word is a state which will permit surgical procedures to be performed without any reaction from, or any dangers to the patient. While thiopentone is one of the best hypnotic drugs known, by modern standards it is an unsatisfactory anaesthetic agent when used alone, except

for very brief procedures. The margin between the dose required for abdominal relaxation and that which will result in apnoea and cardiovascular depression is very small. On the other hand, when used as a hypnotic, thiopentone offers a wide margin of safety and reduces the doses of subsequent drugs.

ADVANTAGES

The advantages of the use of thiopentone are many. Induction of anaesthesia is rapid and pleasant for the patient. It requires the minimum apparatus but a means of inflating the lungs with oxygen or air and an effective means of suction are essential. The agent is non irritant to the respiratory tract and causes no increase in secretions. It may be safely used in the presence of cautery and electrical equipment and avoids the explosion hazard. When its limitations are appreciated and the dosage kept to a minimum, recovery from thiopentone is rapid and nausea and vomiting are uncommon.

DOSAGE

There is no definite dosage of thiopentone which will suit all persons and the requirements of each patient must be individually assessed. The requirements are roughly related to the body weight, and males generally tolerate more than females. Very young patients need large amounts of thiopentone to obtund reflex activity the reverse applying to elderly subjects. Resistance to the narcotic effects of thiobarbiturates is usually encountered in persons who have acquired a tolerance to narcotic and analgesic drugs, but occasionally one may encounter a case of idiopathic resistance

Sensitivity to the narcotic effects of thiopentone occurs in many pathological conditions, especially where there is any interference with diffusion of the drug. The most commonly encountered clinical conditions which induce sensitivity are shock, severe anaemia and uraemia. A combination of one or more of these factors is often found in malaria, ulcerative colitis, malnutrition, intestinal obstruction, severe burns and advanced malignant disease. Delayed recovery may also follow the administration of large doses to patients with hepatic dysfunction, but the degree of liver damage must be very severe before the detoxication of thio-

pentone is impaired. The pre-operative administration of large doses of sedative and analgesic drugs and of some antihistamines reduces the requirements of the narcotic, and intravenous supplementation with analgesic drugs during anaesthesia prolongs the action of thiopentone. Prolonged narcosis usually results when a barbiturate is given for the control of convulsions, and for this reason the dosage should be kept to the minimum necessary to prevent occurrence of the spasms.

Reasons other than the danger of prolonged narcosis may necessitate a reduction in the dosage of thiopentone. In cardiac disease the myocardium is particularly susceptible to its depressant effects; moreover the hypotension resulting from its use may reduce the coronary blood flow to a dangerous level. In peripheral circulatory failure the vasodilatation produced by thiopentone may break the compensatory mechanisms by which an adequate blood supply is maintained to the vital structures. Hypertensive patients or those receiving methonium compounds or chlorpromazine are particularly liable to severe blood pressure falls after thiopentone. In obstetrics, the sensitivity of the foetal respiration to the depressant action of thiopentone necessitates the use of minimal doses of the drug, especially if the baby is expected to be born between 5 and 15 minutes after its administration.

CONTRAINDICATIONS

The absolute contraindications to the use of thiopentone are the same, irrespective of whether it is used for the production of full surgical anaesthesia or as a basal narcotic. However there are many circumstances where its use as sole anaesthetic is not permissible but where, with special care, it can be administered for basal hypnosis. These will be referred to as relative contra-indications. Both the absolute and relative contraindications are listed in Table XLIV.

The **absolute** contraindications to thiopentone are few [illegible] can be divided as follows:

(1) Absence of suitable veins. It is generally agreed [illegible] all anaesthetics the agent should be selected to suit the [illegible] patient. Repeated attempts at venipuncture in a pat[illegible] neither visible nor palpable veins is a violation of [illegible]

not only is it painful for the patient, but serious sequelae may result from the extravenous or intra arterial injection of thiopentone

TABLE XLIV

Contraindications to the use of thiopentone

A. *Absolute Contraindications.* (The drug should not be used either as an anaesthetic or as a basal narcotic.)

(1) Absence of suitable veins.
(2) Unavailability of apparatus to inflate the lungs or perform suction.
(3) Outpatients who have to leave hospital alone.
(4) Inadequate airway before induction.
(5) Factors liable to interfere with the airway during operation.
(6) Certain pathological conditions:

(a) Severe cardiac decompensation.
(b) Severe peripheral circulatory failure.
(c) Severe uraemia.
(d) Porphyria.
(e) Addison's disease.
(f) Status asthmaticus.
(g) Severe herbicidal poisoning

B. *Relative Contraindications.* (The drug should only be used as a basal narcotic and special care taken with its administration.)

(1) Discrepancy between volume of circulating blood and capacity of the vascular bed.
(2) Conditions in which the narcotic effect will be prolonged
(a) Over premedication.
(b) Hepatic dysfunction.
(c) Raised blood urea.
(d) Severe anaemia.
(3) Myocardial weakness.
(4) Raised intracranial pressure.
(5) Slight respiratory obstruction.
(6) Where prolonged periods of muscular relaxation are required.
(7) Children.
(8) Asthma.
(9) Potassium intoxication.
(10) Dystrophia myotonia.
(11) Myasthenia gravis.
(12) Drug addicts.
(13) Untreated myxoedema.
(14) Very severe diabetes.
(15) Adrenocortical insufficiency
(16) Cerebral thrombosis or arteriosclerosis.
(17) Obstetrics.

(2) Unavailability of apparatus with which to inflate the lungs with oxygen or air Although one can usually predict the degree of respiratory depression which follows an induction dose of thiopentone, if prolonged apnoea should occur for any reason apparatus must be available with which to perform artificial respiration. Laryngeal spasm may be initiated by excess mucus or a foreign body during light thiopentone narcosis, and a means of forcing oxygen or air through a semi-closed glottis is essential. Where the spasm results in such severe hypoxia that the use of a short acting muscle relaxant is indicated, artificial respiration following the use of the latter is essential.

(3) Out patients who have not arranged for an escort to

accompany them home. The return of consciousness after thiopentone does not mean that the mental faculties have been completely restored to normal. Patients cannot be held responsible for their actions immediately after recovery from the drug and a period of normal sleep should be insisted upon before patients are left to their own devices.

(4) Mechanical interference with the airway to such an extent that an adequate respiratory exchange can only be maintained with the aid of the accessory muscles of respiration. Once consciousness is lost, the use of the accessory muscles will be abolished and hypoxia result. This is an absolute contraindication to the use of any anaesthetic agent, but once a clear airway has been established thiopentone can be given with safety.

(5) The presence of factors which are liable to interfere with the patency of the airway or lack of access to the airway during anaesthesia. These include a full stomach and operations on the upper respiratory tract. Precautions must first be taken in the latter case to ensure that the airway will not be interfered with during the operation, e.g. by posturing the patient and instituting pharyngeal *suction or by the passage of a cuffed endotracheal* tube. A full stomach must be emptied before anaesthesia is induced with thiopentone. No intravenous anaesthetic should ever be given if it is not possible to perform immediate artificial respiration because of lack of adequate access to the airway.

(6) Certain pathological conditions where severe sequelae may result from the use of thiopentone, irrespective of the care taken in its administration. These include

(*a*) Severe degrees of cardiac decompensation, e.g. constrictive pericarditis.
(*b*) Severe degrees of peripheral circulatory failure.
(*c*) Severe uraemia: patients with blood urea over 200 mg per cent. or already comatose.
(*d*) Porphyria.
(*e*) Addison's disease.
(*f*) Status asthmaticus.
(*g*) Severe herbicidal poisoning.

The relative contraindications, or conditions which necessitate care in the use of thiopentone, are

(1) Any condition which results in a discrepancy between the

volume of the circulating blood and the capacity of the vascular bed, e g severe haemorrhage burns, dehydration, shock and the use of the ganglion blocking agents. Here there is the dual danger of prolonged narcosis and severe hypotension after the use of thiopentone. These effects can be mitigated by the slow administration of small doses of a dilute solution.

(2) Conditions where reduced dosage is necessary to avoid prolonged narcosis. These include moderate degrees of over premedication, uraemia, hepatic dysfunction and severe anaemia. The duration of action of a given dose of thiopentone increases as the blood urea rises and the total duration of sleep is increased out of proportion to the prolongation of the period of surgical anaesthesia. Apart from the dangers of prolonged coma it does not seem wise to administer large doses of a hepatotoxic agent to patients who already have liver damage. In severe anaemia care must be taken to avoid respiratory depression, since cyanosis will not be evident (or may never appear) until a dangerous level of hypoxia is reached.

(3) Myocardial weakness. Here the drug should be given slowly with adequate pauses during the administration respiratory depression should be avoided, and oxygen administered before and during the injection. Prompt measures, such as adoption of the Trendelenburg position and infusion of *l* noradrenaline, should be taken to treat any resulting hypotension.

(4) Raised intracranial pressure. The dangers of the use of thiopentone in this condition are due to the further rise in intracranial pressure which results from hypercarbia, hypoxia, straining and coughing This rise in pressure will depress respiration still further and a vicious circle is rapidly set up It may only be possible to break this train of events by reducing the pressure directly

(5) Slight respiratory obstruction where an adequate respiratory exchange can be maintained without the accessory muscles of respiration but where the profound depressant action of thiopentone may produce severe hypoxia. Injections should be given slowly and a close watch kept on the tidal volume and respiratory rate.

(6) Where prolonged periods of muscular relaxation are required. The dose of thiopentone which will achieve this result is too near the apnoeic dose and a specific muscle relaxant should

be given or anaesthesia continued with a suitable volatile or gaseous agent

(7) Children The hyperactive reflexes of children make them prone to laryngeal spasm or stridor and very deep anaesthesia is required to abolish movements of the limbs in response to stimuli. Thiopentone can be given rectally or intravenously as a basal narcotic, but it should be followed by a supplementary agent.

(8) Asthmatics. The fully active laryngeal and bronchial reflexes which are present during thiopentone anaesthesia increase the likelihood of inducing an attack in these patients Bronchial dilator drugs, or suxamethonium, should always be available, and the dose of thiopentone should never be such as to abolish the effects of carbon dioxide on respiration The use of carbon dioxide prior to the induction of anaesthesia is a valuable aid in reducing the likelihood of laryngeal or bronchial spasm in asthmatics. Full use should be made of the ethers in the subsequent anaesthesia.

(9) Potassium intoxication. There is a rise in blood potassium level during hypercarbia, with a further marked increase when the carbon dioxide is withdrawn. Since thiopentone frequently causes some carbon dioxide accumulation this must be avoided in patients who already have an elevated blood potassium level lest the resulting hyperkalaemia result in ventricular arrhythmias or even in ventricular fibrillation.

(10) Dystrophia myotonia. Even small doses of thiopentone may cause severe respiratory depression in subjects with this disease. A full respiratory volume may not be restored by the time the narcotic effects of thiopentone are wearing off

(11) Myasthenia gravis. Although the action of thiopentone on the normal myoneural junction is of no clinical significance in subjects with severe myasthenia gravis these effects may be exaggerated and respiratory depression follow the use of this drug Doses should be kept to a minimum, and it is usually possible to perform endotracheal intubation after thiopentone alone with the same ease as if a relaxant were also used in a normal person.

(12) Drug addicts. To obtain a desired level of narcosis with thiopentone alone in these patients a dose of the drug may be required which will have dire effects on the cardiovascular system Full use should be made of adjuvants, especially the muscle relaxants

(13) Untreated myoedema. The slow metabolism of these subjects makes them sensitive to all anaesthetics, and delayed recovery is to be expected after large doses of thiopentone.

(14) Severe diabetes. Although thiopentone has a negligible effect on the blood-sugar level, it interferes with the deposition of glycogen in the liver, and hyperglycaemia may result from the administration of glucose prior to induction of anaesthesia. Hypoxia may further raise the blood sugar and deplete the liver glycogen.

(15) Adrenocortical insufficiency and treatment with A.C.T.H. or cortisone. The significance of these factors during thiopentone anaesthesia is not fully understood, but the dosage of narcotic should be kept to a minimum.

(16) Patients with cerebral thrombosis or arteriosclerosis. The hypotension which follows large doses of thiopentone may further increase the area of infarction in persons with recent cerebral thrombosis. In the presence of arteriosclerosis, thrombosis of the cerebral vessels result from prolonged hypotension.

(17) Obstetrics. Very large doses of thiopentone are required to relax uterine tone, and this can be obtained more safely with supplementary agent such as ether Large doses should not be given prior to a forceps delivery or for the operation of Caesarian section. Although the peak concentration of thiobarbiturates in the foetus never reaches that of the maximum maternal blood level after induction, the foetal respiration is particularly susceptible to the depressant effects of the barbiturates. Foetal apnoea may occur if thiopentone is administered to the mother between 5 and 15 minutes before delivery of the baby

ABUSES

There are many ways in which thiopentone can be misused in clinical anaesthesia, other than the administration of large doses where such are contraindicated or its use in the face of an absolute contraindication. The most common of these is the ineffective use of non toxic adjuvants, especially nitrous oxide/oxygen. One frequently sees these serving only as a vehicle for carrying volatile supplementary agents and playing no major part in the anaesthetic sequence. By using a close fitting face mask, or a cuffed endotracheal tube, with large total flows of gases immediately after the

induction of anaesthesia, a concentration of nitrous oxide in the blood sufficient to ensure narcosis is soon obtained, with a corresponding reduction in thiopentone requirements. Pre-oxygenation before the administration of thiopentone makes any subsequent administration of nitrous oxide more rapidly effective. It also permits a longer period of apnoea or respiratory obstruction should any unforeseen accident occur during the induction period

Because of its inability to depress laryngeal reflexes and produce muscular relaxation except with large doses, the use of thiopentone as sole agent for endotracheal intubation seems unwise Reflex responses can be decreased by the use of topical analgesia and muscular relaxation produced by curare-like drugs all of which decrease the doses of thiopentone required for laryngoscopy with obvious benefits to the patient.

The mixing of thiopentone with muscle relaxants, and especially the continued use of dilute solutions of such mixtures, is a practice which is without any scientific basis. The two types of drugs are broken down by different means, and conditions which render patients sensitive to thiopentone often cause resistance to relaxants. In this case an overdose of narcotic can be very easily given. At different periods during an operation either more relaxation or deeper narcosis is needed and with the use of thiopentone-relaxant mixtures one cannot be produced without the other

Mixtures of thiopentone with analeptics are not advised as a routine procedure, even in very poor risk subjects. Nikethamide is a direct myocardial depressant and its main action in anaesthesia is to minimise respiratory depression even this effect is only transient. Mixing thiopentone with methamphetamine (Methedrine) also seems unwise, since the latter drug does not effectively counteract the vasodilatation caused by thiopentone but only flogs the heart which is already depressed by the barbiturate. If it is felt that a vasopressor drug should be given, as in patients who are already hypotensive or where anaesthesia must be induced with the patient sitting up a pure vasoconstrictor with minimal direct action on the heart should be used. The most satisfactory drugs in this respect would appear to be methoxamine and phenylephrine.

A not uncommon use of thiopentone is for the minor operation which takes longer than originally anticipated. The use of

an adjuvant should never be delayed more than 5 to 10 minutes after induction. This applies especially where the stimulus is strong as for example during distension of the bladder or where profound relaxation is required, as in reduction and plastering a fracture. Large doses are often followed by delayed recovery. The patient may appear to be lightly anaesthetised when the stimulus is present, but on return to the ward may relapse into deep unconsciousness and be exposed to all the dangers of respiratory obstruction and depression.

The rapid injection of moderate doses of thiopentone to produce a short period of good relaxation is a practice which is not without danger. The effects on the cardiovascular system depend upon, among other factors, the absolute concentration of the drug in the blood stream. While the intact cardiovascular system can accommodate itself to the effects of the usual concentrations which are achieved during induction, one has no way of telling whether it can stand up to large amounts. The high concentration of the drug achieved with the above technique will have a profound effect on the blood pressure and cardiovascular system in general, if there is any cardiac disease. The safety of thiopentone is decreased enormously by a rapid rate of injection.

DANGERS

Every intravenous injection carries the dangers of infection and breakage of needles and haematoma formation. Infection is more likely to result from contamination of the needle and syringe than from the skin, although the latter must be cleaned by methylated ether or spirit. Cross-infection can be prevented by proper cleaning of syringes, followed by boiling in alkaline water autoclaving or steam sterilisation. Breakage of needles is most likely to result from movement of the limb during or after the induction of anaesthesia. Spontaneous movement is a manifestation of the second stage of anaesthesia, and its incidence and intensity can be reduced by premedication with an analgesic drug. Haematoma formation after withdrawal of the needle is commonly the result of an inadequately released tourniquet or constriction of the limb by clothing. An injection of hyaluronidase will help to disperse the blood, but strict asepsis must be observed.

The local irritant action of thiopentone results in tissue

necrosis if a large amount of solution is deposited in the subcutaneous tissues. The more concentrated the solution the greater will be the likelihood of untoward sequelae An immediate infiltration of the affected part with procaine and hyaluronidase must always be carried out after an extravenous injection

The high alkalinity of thiopentone solutions results in spasm and sometimes thrombosis of arteries, if such vessels are entered in mistake for veins. Too tight a tourniquet may occlude the peripheral arterial pulsation and the expected flow of bright red blood into the syringe is rare. Intra arterial injection of thiopentone is generally followed by an intense pain shooting down the arm, but this may be absent. The radial pulse may become impalpable, and blanching of the arm and fingers occurs The ultimate prognosis depends on the tissues to which the thiopentone has been distributed, whether the drug causes an immediate thrombosis of the artery or only spasm and the intensity of the treatment. If possible the needle should be left in the vessel and a dilute solution containing 40 to 80 mg papaverine injected into the artery Procaine should be used if papaverine is not available. Rather than cause further trauma by trying to reinsert the needle into the artery if it has been removed the area round the vessel should be infiltrated with papaverine A brachial plexus block should be carried out with ½ per cent. lignocaine, and during this injection it is an easy matter to inject papaverine into the subclavian artery Immediate heparinisation should be carried out, unless there is some contraindication and for this reason all except the most urgent operations should be postponed. Subsequent anaesthesia should be with vasodilator agents such as cyclopropane and ether Where this treatment is not effective in completely alleviating the condition it may be necessary to cut down and remove the clot from the artery at a later date.

The sequelae after the intra arterial injection of thiopentone are reduced by the use of a dilute solution and this should be employed where the vein is not clearly visible. Palpation before application of the tourniquet will reveal the presence of an aberrant artery which is present in about 10 per cent. of subjects, and is most commonly found on the medial side of the antecubital fossa. This site should not be used for injections unless the veins are clearly seen. A preliminary injection of not more than 2 ml. solution, followed by a pause of 10 to 15 seconds, is recommended

an adjuvant should never be delayed more than 5 to 10 minutes after induction. This applies especially where the stimulus is strong as for example during distension of the bladder or where profound relaxation is required, as in reduction and plastering a fracture. Large doses are often followed by delayed recovery. The patient may appear to be lightly anaesthetised when the stimulus is present, but on return to the ward may relapse into deep unconsciousness and be exposed to all the dangers of respiratory obstruction and depression.

The rapid injection of moderate doses of thiopentone to produce a short period of good relaxation is a practice which is not without danger. The effects on the cardiovascular system depend upon, among other factors, the absolute concentration of the drug in the blood stream. While the intact cardiovascular system can accommodate itself to the effects of the usual concentrations which are achieved during induction, one has no way of telling whether it can stand up to large amounts. The high concentration of the drug achieved with the above technique will have a profound effect on the blood pressure and cardiovascular system in general, if there is any cardiac disease. The safety of thiopentone is decreased enormously by a rapid rate of injection.

DANGERS

Every intravenous injection carries the dangers of infection and breakage of needles and haematoma formation. Infection is more likely to result from contamination of the needle and syringe than from the skin, although the latter must be cleaned by methylated ether or spirit. Cross-infection can be prevented by proper cleaning of syringes, followed by boiling in alkaline water autoclaving or steam sterilisation. Breakage of needles is most likely to result from movement of the limb during or after the induction of anaesthesia. Spontaneous movement is a manifestation of the second stage of anaesthesia, and its incidence and intensity can be reduced by premedication with an analgesic drug. Haematoma formation after withdrawal of the needle is commonly the result of an inadequately released tourniquet or constriction of the limb by clothing. An injection of hyaluronidase will help to disperse the blood but strict asepsis must be observed.

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as a routine in all injections. This will show whether the patient experiences any pain, and the amount of solution is not likely to have any permanent harmful effects.

Injection into the medial side of the antecubital fossa carries the hazard of affecting the median nerve. This will also be followed by severe pain in the fingers and the immediate injection of procaine and hyaluronidase should be carried out.

The general effects of thiopentone are the result of an overdose which Nosworthy has described as being "fatally easy to give". It usually results from the lack of appreciation of the limitations of the drug, but occasionally may be caused by a tight constriction above the site of the injection.

Cardiovascular collapse is the most serious of the many effects of an overdose of thiopentone and is the one which is most difficult to treat. Immediate lowering of the head of the table may be all that is required, but failure of the patient to improve after this is an indication for the use of a vasoconstrictor such as *l* nor adrenaline infusion. Any blood loss should be replaced as soon as possible, but over transfusion must be avoided.

Since apnoea or respiratory depression frequently accompanies cardiovascular collapse, artificial respiration should be carried out with oxygen. Carbon dioxide plays no part in the treatment of respiratory depression in deep barbiturate narcosis, save to ensure that apnoea is not being maintained by hypocarbia. Analeptics are not recommended, and by increasing the cerebral oxygen consumption they may even be harmful.

Laryngeal spasm may occur during the induction period, especially if the patient has not been adequately atropinised or if an airway or laryngoscope blade is introduced before the laryngeal reflexes are obtunded by a supplementary agent, topical analgesia or a muscle relaxant. Minor degrees of spasm can be relieved by deepening the anaesthesia and by forcing oxygen under pressure into the patient. Unless prompt action is taken, the congestion which results from the spasm may further increase the respiratory obstruction and a vicious circle will be set up.

Complete closure of the glottis was once a major hazard in the use of thiopentone, but the situation has changed since the introduction of the rapid-acting muscle relaxants. One should not hesitate to inject 50 mg suxamethonium where the spasm is persistent, but it is necessary first to ensure than the pharynx is

not full of regurgitated stomach contents Bronchospasm is rare after thiopentone and a more likely cause for difficulty in inflating the patient should be sought before this diagnosis is made. Such causes include a kinked or blocked endotracheal tube reflex muscle spasm involving the diaphragm and intercostal muscles or some fault in the anaesthetic apparatus The treatment for reflex muscle spasm and true bronchospasm is to use suxa methonium or inject more thiopentone where this is permissible. With both bronchospasm and larnygeal spasm it is essential to deepen the anaesthesia, preferably with an ether during the period of apnoea following the suxamethonium, and 10 to 30 mg peth idine may be given intravenously

Delay in recovery after thiopentone should be treated as for barbiturate poisoning The principles of this are adequate oxygenation and support of the circulation. If oxygen is given in an open or semi-open circuit, it should first be humidified, and care must be taken to see that secretions are not allowed to accumulate in the tracheo-bronchial tree. Analeptics are only permissible when the coma has become very light and where there is no concomitant cardiovascular depression. It is essential to ensure that it is the anaesthetic which is causing the delay in recovery and not some other factor such as increased intra cranial pressure or a cerebro-vascular catastrophe.

Respiratory obstruction from relaxation of the jaw muscles and the tongue falling back against the pharyngeal wall can occur after thiopentone as easily as after any other anaesthetic agent. Care should be taken not to insert a pharyngeal airway during too light narcosis, lest an attack of laryngeal spasm be initiated. Where the obstruction cannot be overcome by supporting behind the angle of the mandible with the fingers (or when this support cannot be maintained by the anaesthetist for other reasons) a naso-pharyn geal airway should be inserted. If this does not produce a clear airway and the operation is likely to be a long one, or if the patient is in such a state that even temporary slight hypoxia and hypercarbia are not permissible, a muscle relaxant should be given and an endotracheal tube passed. The necessity of using a relaxant can be overcome by spraying over the back of the tongue with 4 per cent. lignocaine after induction

Respiratory obstruction when the patient has been returned to the ward is more common after the use of thiopentone than after

inhalation anaesthesia. Removal of the surgical stimulus results in a deepening of the clinical level of anaesthesia, and unless there is some very definite contraindication, the patient should be placed on his side in the so-called 'tonsil position'.

Post-operative excitement after thiopentone is more common in children than in adults. It is a manifestation of the second stage of anaesthesia or of the lack of analgesic properties of the drug. While it does not last as long as when a medium acting barbiturate is used, it may be very troublesome and an analgesic should be given.

Damage to the brachial plexus, by stretching, may result from abduction and extension of the arm when the patient is in the Trendelenburg position. This danger is increased by external rotation of the forearm, by the use of shoulder rests and allowing the arm to fall behind the coronal plane. If intravenous supplementation of anaesthesia is required with the patient in this position, the arm can be placed across the chest, an intravenous infusion can be set up and the arm placed at the side of the patient, or the veins of the foot can be used.

SOLUTIONS

Thiopentone should be made up for single dose or intermittent use in a 2·0 to 5 per cent. aqueous solution. In a closed container at room temperature these keep for 48 hours and in a refrigerator for up to 7 days. Solutions should not be used which show any cloudiness or discoloration. Mixing should be thorough as the solution at the top of the ampoule or bottle may be less concentrated than desired, with a more concentrated solution at the bottom. Random samples of solutions of thiopentone prepared for anaesthesia taken from various sources show a wide variation from the expected concentration. While this may be unimportant to an experienced anaesthetist who can judge the requirements on the response to the initial dose, in conditions of sensitivity an overdose can be given easily by the use of a more concentrated dose of solution than intended.

A 5 per cent. solution (1 g. in 20 ml.) is most commonly used for routine anaesthesia in this country. However, the 2·5 per cent. solution is safer in many respects. It is less irritant to the tissues and severe sequelae are less frequent following its extravenous

or intra-arterial injection More control can be exercised over the dosage, and if a narrow bore needle is used, the likelihood of too rapid injection is minimised As a 2 5 per cent. solution is recommended for elderly and poor risk subjects, it seems wise to use this strength as a routine for all patients Should any undue sensitivity to thiopentone be shown during the induction the slow injection will minimise the untoward effects and impeding collapse may be detected before the condition becomes serious The necessity for larger volumes of solutions and a greater number and sizes of syringes is a minor disadvantage, as is the fact that most manufacturers only supply sufficient water with the thiopentone to make 5 per cent. solution These difficulties are more than compensated for by the increased safety which a 2 5 per cent. solution offers.

ADMINISTRATION

There are several precautions which should be observed before and during the intravenous administration of thiopentone

(1) If atropine or hyoscine has not been given or if it is more than 3 hours since its administration, give atropine $\frac{1}{100}$ gr (0·65 mg) intravenously to adults before the thiopentone, unless there is some contraindication to its use.
(2) Where possible, choose a vein outside the antecubital fossa, and especially avoid its medial side, for the injection.
(3) Inspect and palpate the injection site before the tourniquet is applied.
(4) Do not apply a tourniquet sufficiently tightly to occlude the arterial pulsation
(5) Check that the tourniquet is properly released before the injection
(6) Be sure that there is a free flow of blood on aspiration
(7) Do not inject more than 2 ml. solution (irrespective of its concentration) as a preliminary, unless the injection is being made into an intravenous infusion Pause for a few seconds after this injection to allow the effects of an inadvertent intra arterial injection to be manifest.
(8) Do not continue to inject thiopentone once apnoea has occurred.

Before any administration of thiopentone one must decide

whether the drug is to be used as an anaesthetic or as a basal hypnotic. This will affect the method of administration and dosage.

Since the use of thiopentone as a sole anaesthetic is reserved fit persons, and since transitory relaxation may be required, a mo rapid rate of injection is permissible. The injection should not b commenced until the surgeon is ready and all instruments, etc. are prepared. For complete anaesthesia, about two to three times the dose which produces sleep will be required, and frequent increments are necessary to maintain a satisfactory depth of anaesthesia. After the preliminary 2 ml. of solution and the subsequent pause, the injection should be continued slowly until consciousness is lost. The total dose given is noted, and after another brief pause an equal volume is injected at a more rapid rate. This will invariably produce apnoea. If however the patient should move when stimulated, a pause of 15 seconds should be allowed for its full depressant effect to be observed, and if the operation is still not possible, the sleep dose should be repeated. Further increments will depend on the nature of the operation and the physical state of the patient. They will be less as time proceeds and should be timed to produce their maximum effect when the stimulus to the patient is strongest.

It must be pointed out again that the use of thiopentone as a sole anaesthetic agent should be reserved for the fit patient. It is not a technique for the inexperienced anaesthetist. If the oper ative procedure is prolonged for more than a few minutes, a large flow of nitrous oxide-oxygen should be given. A large gas flow aids the removal of the alveolar nitrogen and increases the efficacy of the nitrous oxide. Care should be taken to ensure that respir atory obstruction does not occur when the relaxation is maximal. While a variable period of apnoea is inevitable with the above technique, if it is prolonged for more than one minute in the fit subject, the lungs should be inflated with nitrous oxide/oxygen. There is no maximum dose of thiopentone, but 1.5 g should rarely be exceeded. If the patient proves to be unduly resistant, or if the operation lasts more than 5 to 10 minutes a powerful volatile or gaseous supplement should be used.

The induction dose of thiopentone for basal narcosis should not exceed 50 mg per stone (14 lb.) The same technique as above is advocated, but the repeat of the sleep dose after consciousness

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has been lost should be given slowly to prevent respiratory depression and thus facilitate the introduction of supplementary inhalation agents. Supplementary doses should be smaller than when the drug is used alone, and the rate of injection should also be slower

Where a long acting muscle relaxant is to be used for intubation during induction of anaesthesia a test dose should be given before consciousness is lost. If the injections are being given into an intravenous drip or if the needle is securely placed in a vein, the full dose of relaxant should be given before the thiopentone so that the maximum effect of the two drugs is obtained at the same time and intubation facilitated. This injection of relaxant before narcotic should never be employed if there is any possibility of the needle coming out of the vein or one may produce a curarised but conscious patient. If suxamethonium is to be used to facilitate intubation, it should be injected after the thiopentone to prevent the patient being aware of the muscle twitchings that occur during depolarisation Even the practice of mixing thiopentone and suxamethonium does not always prevent the patient from remembering the uncomfortable muscle twitchings.

Nitrous oxide/oxygen is the safest agent with which to continue the anaesthesia after thiopentone, and the effective use of this mixture will reduce the requirements of supplementary drugs A narcotic concentration of nitrous oxide in the blood can be obtained rapidly by the use of large flows of gases. It is never necessary to reduce the oxygen concentration to hypoxia levels to produce this effect. On the contrary, it is advised that mixtures containing more than 20 per cent. oxygen be employed as a routine This will reduce the hypoxic stimulus which is necessary for respiration in deep anaesthesia thereby reducing the possibility of undetected respiratory depression Even when closed-circuit anaesthesia with carbon dioxide absorption is employed, large flows of gases should be given after induction and a satisfactory maintenance mixture is 2 litres of nitrous oxide and 1 litre of oxygen per minute.

Difficulty may be encountered in obtaining a smooth continuity of anaesthesia after thiopentone and suxamethonium have been used for endotracheal intubation This is due to the reflexes which arise from the stimulus of the tube during light thiopentone narcosis after the effects of the relaxant have worn off Coughing

breath holding or even bronchospasm may occur These can be minimised, or often completely abolished, by the effective topical application of 4 per cent. lignocaine to the larynx and trachea. During the period of apnoea, inflation of the lungs should be carried out with the supplementary anaesthetic agents, such as nitrous oxide/oxygen/ether or trichlorethylene, or cyclopropane/oxygen, and not with oxygen. Pethidine in doses of 20 to 25 mg may be given immediately after the relaxant and will be exercising its maximum action in depressing laryngeal reflexes by the time the suxamethonium has worn off. If coughing or breath holding occur a small dose of thiopentone can be given, and this is probably the only circumstance in which this drug is injected for the treatment of apnoea.

When the thiopentone-suxamethonium combination is used to obtund the convulsions of electro-convulsive therapy special precautions must be observed. The dose of thiopentone which is necessary to produce unconsciousness will often raise the threshold to convulsions so that two or three shocks of increasing voltage may be required. Since all that is required from the thiopentone in this technique is to produce amnesia to the effect of the relaxant, the doses given should rarely exceed 200 mg

When thiopentone is given to supplement spinal or local analgesia, it is only necessary to maintain a light level of narcosis, and very small doses should be given. An airway should not be required. However, the patient may tire, especially if the arms are strapped to an arm-board or if shoulder rests are used. This will lead to large doses of narcotics being required, and this is undesirable, especially towards the end of an operation. The judicious use of small doses of analgesics will help to mitigate this necessity for large doses.

Thiopentone should never be used alone to cover the deficiencies of ineffective spinal or local analgesia. In spite of this, small doses of thiopentone will often enable operations to be carried out when this is not possible from the local analgesia alone, as the conscious patient may interpret the sensation of touch as indicating pain. This is probably the reason why light narcosis often markedly prolongs the duration of analgesia, as the sensation of touch will return before that of pain.

RECTAL USE

Thiopentone is useful as a basal narcotic, given by the rectal route, for children It is particularly indicated for procedures such as cystoscopy minor operations cardiac catheterisation, lumbar puncture and dressing of burns. It may be possible to obtain a sufficient depth of narcosis for these short procedures with thiopentone alone, but one can follow it with any supplementary agent desired

The usual dose is 1 g per 50 lb body weight (20 mg /lb) given in a 2 5 or 5 per cent solution With the small volume of solution required there is less likelihood of it not being retained in the rectum than with bromethol or paraldehyde. An enema is not essential before its administration, but where this is being given as a routine before operation it should consist of tap water or saline in preference to soap-suds, and should be so timed as to allow 6 hours before the thiopentone is given. Atropine is essential and should be given subcutaneously about 1 hour before the thiopentone. Opiates or oral barbiturates are not recommended in combination with rectal thiopentone. The patient should be prepared as for any general anaesthetic.

After the above dose, consciousness is lost within 5 to 15 minutes and the maximum effects last for about another 20 to 30 minutes Consciousness is usually returning 1 hour after administration of the drug The clinical picture is the same as after a very slow intravenous induction with thiopentone. The slow absorption into the blood stream minimises the depressant effects on the blood pressure, but respiratory depression and relaxation of the jaw occur, and the patient should not be left alone on his back. It is advisable to turn the patient on the left side during the administration, and he should remain in this position until taken to the operating theatre. If obstruction of the airway still occurs, even in the lateral position, an oro-pharyngeal or naso-pharyngeal airway should be inserted. Laryngospasm may occur when rectal thiopentone is used alone for minor procedures where the degree of stimulation is great. Supplementation of the narcosis is necessary in these patients before the operation commences. Where the operation has been painful there may be some restlessness during recovery but this can be controlled with a subcutaneous injection of pethidine or nepenthe.

The circumstances where rectal thiopentone should be avoided are shown in Table XLV Rectal anaesthesia with any agent is

TABLE XLV

Contraindications to the rectal use of thiopentone

(1) Contraindications to any form of rectal narcosis.
(2) Absolute contraindications to thiopentone.
(3) Unavailability of staff to see that respiratory obstruction or depression does not occur
(4) Where a prompt return of reflexes is required at the end of the operation.
(5) As the sole agent, where diagnostic or surgical procedures are particularly stimulating
(6) It is advisable to avoid its use in the presence of a relative contraindication to thiopentone.

contraindicated in operations on the rectum and lower bowel. It should not be used in the presence of disease of these structures One is not as likely to encounter any of the absolute contraindications to thiopentone in the age-group for whom the rectal route of administration is advocated, as in adults Since the total amount to be administered must be calculated beforehand, and since the reduction in this dosage will only produce a semi comatosed and possibly an excited patient, it is advisable to avoid the rectal administration of thiopentone in the presence of any of the relative contraindications listed in Table XLIV This method *of induction of anaesthesia should not* be used *where it is essential* to have a rapid return of the cough reflex at the end of the operation. This applies particularly to such procedures as tonsillectomy and curettage of adenoids.

INTRAMEDULLARY ADMINISTRATION

The sternal route has been suggested for the administration of thiopentone or parenteral fluids where the intravenous route is impracticable. Because of the rich blood supply of the red bone marrow the onset of narcosis will be almost as rapid as after intravenous injection. The continuous infusion of a dilute solution of thiopentone (0·3 *to* 0 5 per cent.) *is advocated if this* route is adopted, in preference to the intermittent injection.

A large-bore winged needle is employed for injection. Strict asepsis must be employed in its insertion which is carried out under local analgesia. A skin weal is raised in the midline over the second inter costal space and infiltration carried out down to the periostium.

After the skin is nicked the needle is passed down to the outer plate of the sternum which is pierced with a boring action. Aspiration of material resembling blood indicates that the needle point is correctly placed. This aspiration usually causes some discomfort to the patient. A few ml of sodium citrate solution are injected to clear the needle, and the continuous-drip apparatus is connected. Positive pressure is usually necessary to produce a steady flow.

The intramedullary route carries a high incidence of osteomyelitis and sepsis. The inner plate of the sternum may be pierced, and this is often followed by mediastinitis. The dangers of this technique are greater than the advantages of the administration of thiopentone in patients without suitable veins. It is rarely, if ever indicated as a method of producing anaesthesia, although it may be useful for the infusion of blood (or plasma). The introduction of hyaluronidase, permitting subcutaneous infusion, has eliminated the necessity of employing the sternal route for the administration of electrolytes or dextrose in patients who have no suitable veins.

THIOPENTONE-PROCAINE MIXTURES

This is included in this section for the sake of convenience. The idea of combining a dilute solution of thiopentone with intravenous procaine was conceived by Fraser (1948). The object was to use the procaine for its analgesic properties and to prevent cardiac arrhythmias. The intravenous use of procaine as an analgesic has had much popularity in the treatment of burns and for post-operative sedation. The drug is known to be nearly as active as quinidine in reducing cardiac irritability. When very large doses of procaine are infused a central effect may be obtained: patients are analgesic, fairly relaxed, but appear mentally to be far away (Allen, 1946).

A combination of 1 to 2 g. thiopentone and 0·5 to 1 g. procaine in 1 litre of dextrose or normal saline does not form a precipitate. This is combined with nitrous oxide/oxygen or cyclopropane/oxygen, and with a muscle relaxant if required. Fraser and Kraft (1948) have reported on this technique in a large series of poor risk patients, and apart from one case of convulsions during its use, the results were very satisfactory. For post-operative analgesia the drip is continued but the amount of thiopentone is reduced to 0·5 g. per litre. Soares (1952) has modified the above technique by using a continuous infusion of procaine and the addition of thiopentone as required. This would seem to give more controllable anaesthesia.

The introduction of pethidine as an intravenous supplement during anaesthesia, and the growing appreciation of the analgesic values of non-hypnoxic mixtures of nitrous oxide and oxygen, have led to the

almost complete abandonment of thiopentone/procaine mixtures. However where nitrous oxide is not easily available, and it is not desired to use large doses of pethidine because of the dangers of respiratory depression, intravenous procaine is useful as an adjuvant to thiopentone. It is recommended that the drugs be given separately as described by Soares.

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CHAPTER X

SOME NEWER THIOBARBITURATES

DURING the past few years numerous barbiturates and thiobarbiturates have been synthesised and their narcotic properties investigated by animal experiments. The object of introducing these compounds appears to be the finding of a drug similar to but with a shorter recovery time than, thiopentone. It will be seen that this is claimed for many of the compounds which have been subjected to clinical trial Unfortunately in some instances this brevity of action is accompanied by a higher incidence of side-effects, which more than outweighs any advantages to be obtained from the compounds. Until more detailed studies have been completed on their pharmacology, it is recommended that the contraindications to the use of thiopentone be applied to these newer compounds and that the precautions which are taken with thiopentone be adhered to with all thiobarbiturates.

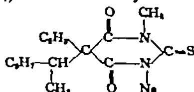
N METHYL AND *N*-ETHYL THIOBARBITURATES

Many hundreds of these compounds have been prepared in the hope that the replacement of the oxygen by sulphur, and alkylation of nitrogen, might result in products having an even shorter action than thiopentone.

Some of these drugs haemolyse mammalian blood and a few have a convulsant action

The toxicity and duration of action of four *N* methyl derivatives have been studied by Swanson and Chen (1953) In most of the animals employed the $A.D_{50}$ and $L.D_{50}$ were similar to those for thiopentone and thiamylal in the same species. Fig 14 shows that the *N* methyl thiobarbiturates have less cumulative action than their parent thiobarbiturates. This suggests a more rapid rate of breakdown

N methyl thiopentone (Lilly 14694) has been found by Stoelting (1953) and Stoelting and Graf (1954) to have about half the duration of action of thiopentone in dogs. In man narcosis was extremely profound and of very



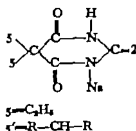
thiobarbiturates (*spiro*-[2-ethyl 3 5-dimethylcyclopentane]-5 5 pyrimidine-2 thio-4,6-dione sodium) (Spirothal) has been employed with decamethonium for endotracheal intubation A rather high incidence of laryngospasm and bronchospasm was reported with this combination.

THIONARCEX (J.L. 1074)

Thionarcex was first described by Kopp and Tchoubar (1951) It is the sodium salt of 5-ethyl 1 butyl 5 thiobarbituric acid, its oxygen analogue being known as Butylaedal (J L 991) (Table XLVIII) Buchel and Levy (1951) and Buchel, Levy and Tchoubar (1953) have prepared a large number of compounds

TABLE XLVIII

Thionarcex and similar compounds



Compound	R	R	x
Butylaedal (J.L. 991)	C_3H_7	C_2H_5	O
Thionarcex (J.L. 1074)	C_3H_7	C_2H_5	S
J.L. 1179	CH_3	C_4H_9	O

with similar side chains. They found that when the 5 -(R—CH —R′) radical contained 5 to 8 carbon atoms, a compound was produced from which recovery was almost instantaneous. A rather surprising finding was that substitution of an ethyl or propyl grouping in the (R—CH—R′) side-chain endowed the compound with some analgesic properties.

Thionarcex is prepared for use in a 2 5 per cent. solution, the powder being less soluble than thiopentone, but more so than thialbarbitone. Reports on its use in anaesthesia by Amiot (1952) Thuillier (1953) Jaquenoud (1953) Meirsman Roobroeck (1953) and Vincent (1954) are encouraging The addition of the extra CH_2 in the side-chain appears to have produced a drug from which recovery is slightly more rapid than from thiopentone. This advantage does not seem to be accompanied by any increase in the number of complications. Clinical results suggest that Thionarcex is about 20 per cent. more powerful than thiopentone.

Another similar compound 5-ethyl methyl 5 pentyl barbiturate (J L 1179) although neither a *thio*barbiturate nor a *N methyl* barbiturate was found by Buchel and Levy (1953) to have a duration of action comparable with that of thiopentone and hexobarbitone. While slightly more toxic than these drugs, it was reported to possess some analgesic properties

BAYTINAL (TRANSITHAL, Buthalitone)

The sodium salt of 5 allyl 5′ isobutyl barbituric acid (Table XLIX) was first described by Miller, Munch, Crossby and Hartung in 1936 but was not subjected to clinical trial for almost another twenty years. Its pharmacology has been investigated by Weese and Koss (1954)[1] mainly in dogs and rabbits Experiments with the heart lung liver preparation showed that Baytinal is detoxicated in the liver Doses of 40 mg/kg showed very little cumulative action in the rabbit. Histological examination revealed no demonstrable change in the organs of animals to which the drug was administered daily for 13 days. As with all similar drugs, respiratory depression followed the use of Baytinal. The drug had no significant effect on the blood volume in dogs, but a slight transient hypotension followed its use. Changes in blood sugar were negligible and blood coagulation was unchanged during narcosis with Baytinal.

TABLE XLIX

Formulae of three new thiobarbiturates

(General formula: barbiturate ring with O, H, C=S, N, Na; substituents 5 and 5′)

	5	5′
Baytinal	CH_2—CH=CH_2—	CH_3 CH_3 >CH—CH_2—
Inactin	CH_3—CH_2—	CH_3—CH_2 CH_3 >CH—
Thiogenal	CH_3—CH_2—CH_2—CH(CH_3)	CH_3—S—CH_2—CH_2—

[1] This was the last contribution made to anaesthesia by Hellmuth Weese (1897 1954), who introduced hexobarbitone.

Thiogenal would eliminate the necessity of watching patients after thiobarbiturate narcosis.

Clinical reports have shown that recovery from Thiogenal is usually rapid. Ludorg and Schwier (1955) used it for minor surgery and sent the patients home about 45 minutes after the operation. Jacob (1954) has found it satisfactory for bronchoscopy in tuberculous patients. Bunka (1954) Paradowski (1954) Fusslin, Kaniak and Wierners (1954) Benolken (1955) and others have all confirmed this brevity of action of Thiogenal, but its use has not yet been reported in this country The author has used the drug in over 100 cases and has been impressed by the extremely rapid recovery from effective-narcotic doses. However a high incidence of respiratory disturbances, such as coughing and *hiccough, occurred in these patients, and these were of such* severity as to outweigh the advantages from its short action.

It will be noted that in the clinical reports on the use of the above drugs, all the emphasis has been placed on their short duration. Delayed recovery is extremely rare after thiopentone, provided the limitations of this drug are fully appreciated Of greater value would be the synthesis of a preparation which produced equally satisfactory anaesthesia as thiopentone, but which lacked its irritant action on the subcutaneous tissues and arteries and was less depressant to the cardiovascular and respiratory systems.

A drug enabling out patients to benefit from the pleasant induction which thiopentone offers would be very welcome, provided the recovery time is short. On this criterion alone, some of the above drugs would seem to have a place in modern anaesthesia. However anaesthesia for minor operations is generally entrusted to the most junior members of the anaesthetic staff or to the newly qualified house surgeons. This situation is highly unsatisfactory since some of the out patient anaesthetics are the most difficult in the hospital. Even if recovery from thiopentone itself were more rapid it could not be recommended as a routine drug to such inexperienced personnel. A brief period of cyanosis from nitrous oxide/oxygen or a short struggle during the induction stage is to be preferred to hypotension, aspiration of vomitus, sloughing of subcutaneous tissues or the sequelae of intra-arterial injection. It is to be hoped that the investigators to whom are entrusted the

clinical trials of new thiobarbiturates will be extremely rigorous in their criteria for a satisfactory intravenous anaesthetic, and will not recommend the universal use of a drug on the sole grounds of its brevity of action It has been said that the disasters after chloroform were more common in patients who were having minor operations unless the new thiobarbiturates are thoroughly studied, before being made available commercially, this statement might well apply in the future to intravenous anaesthesia.

OTHER NEW DRUGS

Despite their many disadvantages the barbiturates and thiobarbiturates hold an unrivalled position in intravenous anaesthesia. Although many non barbiturate sedatives and hypnotics have been synthesised in recent years, only two drugs seem likely to be of value in anaesthetic practice.

STEROIDS. The observation made by Selye (1941) that certain steroids produce cerebral depression in experimental animals led to the development of 21 hydroxypregnane 3 20-dione sodium succinate (Viadril P 55) This drug possesses anaesthetic properties in man and in therapeutic doses is practically devoid of endocrine activity Its effects on cerebral metabolism are almost identical with those of barbiturate anaesthesia.

Laubach *et al* (1955) found Viadril to have a therapeutic index (L.D 50 A.D 50) of 11 5 in the mouse and rat, as compared with 4 for thiopentone. It was not as potent as thiopentone in monkeys and cats, while the action of the two drugs was similar in the dog

Viadril is a water-soluble white crystalline substance, aqueous solutions having a *p*H of 8 5 to 9·8 It is prepared for use in a 2 5 per cent. solution. In man the drug must be injected into a freely running infusion of 5 per cent. dextrose, and sufficient dilution takes place so that the concentration entering the vein does not exceed 1 25 per cent. Pain on injection follows the use of more concentrated solutions.

Murphy Guadagni and De Bon (1955) reporting their experiences in 125 cases, found that the anaesthetic dose of Viadril varied with the weight, age and physical condition of the patients. The majority of their subjects received 1000 to 1500 mg., given over 5 minutes. Unlike thiopentone, the onset of sleep was delayed for 5 to 10 minutes after injection, but was a smooth quiet process, devoid of any excitement phase. Anaesthesia was continued with nitrous oxide (oxygen) pethidine and muscle relaxants if required. The maximum effect of Viadril usually lasted for about two hours after which it was often necessary to administer a smaller dose than that used for induction.

The ability of Viadril to obtund pharyngeal and laryngeal reflexes

usually allowed endotracheal intubation to be carried out without a relaxant. Transient laryngospasm may follow unsuccessful attempts at intubation, and once the tube is inserted there may be some coughing which usually subsides in less than a minute. The analgesic properties of Viadril were demonstrated by the smaller doses of pethidine required to supplement anaesthesia, as compared with thiopentone. It also appeared to produce better muscular relaxation than the latter drug, and controlled respiration could be instituted without difficulty. These latter two effects may however be due to the difference in duration of action of Viadril and thiopentone.

Guadagni (1955) has remarked that, unlike thiopentone, Viadril is probably not just a hypnotic, but a true anaesthetic agent. Unfortunately its irritant properties make phlebitis a potential complication of the administration, and a slight transient blood pressure fall usually accompanies its use.

Dolitrone (5-ethyl-6-phenyl-meta thiazine-2 4 dione), an analgesic in small doses, can produce surgical anaesthesia if sufficient is injected intravenously. It is administered in a suspension in 50 per cent. polyethylene glycol 200. One gramme given intramuscularly in 10 ml. solution, will relieve pain for about two hours in an adult. Lundy (1955) has used Dolitrone for oral surgery and found little or no laryngospasm with anaesthetic doses. Unfortunately like Viadril, the drug is irritant to veins, and phlebitis is liable to follow its use.

Although little is known, as yet, about these non-barbiturate intravenous anaesthetics, it will be seen that, in their present form neither drug appears to offer any major advantage over the thiobarbiturates. However they open up possibilities with completely new types of drugs, and with subsequent modifications of their formulae, it may be possible to obtain anaesthetic agents which do not possess the hazards of the thiobarbiturates.

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CHAPTER XI

ANALEPTICS AND OTHER STIMULANTS

IT is not proposed to discuss all the drugs which come under this heading but to describe some of the important properties of the most useful and most recent, of these. This chapter will be limited to drugs which can be given intravenously during anaesthesia.

ANALEPTICS

The modern use of analeptics dates from the work of Maloney, Fitch and Tatum (1931) with picrotoxin. They found that this drug antagonised the central depression which resulted from large doses of barbiturates, and that it was more effective than nik ethamide. Maloney and Tatum (1932) and Maloney (1933) showed that picrotoxin was as effective in man as in animals. However Veal and Hamilton (1936) found that neither picrotoxin, nikethamide, lobeline nor leptazol were able to antagonise lethal doses of hexobarbitone. In man, Koppanyi, Linegar and Dille (1936) found that picrotoxin and leptazol produced a wakening effect if minimal doses of barbitone or pentobarbitone were given, but in animals under deep anaesthesia the stimulants could be pushed to the point of convulsions without a return of consciousness. This agrees with the observations of Mousel and Essex (1941) who found that nikethamide, metrazol and lobeline and picrotoxin caused some stimulation during light thiopentone anaesthesia but had no effect, or might even be harmful, in deep narcosis. This statement summarises the widely accepted present day view on the value of analeptics

The position regarding the use of analeptics in barbiturates overdosage has been reviewed in pages 173 4. To this may be added the following statements by Goodman and Gilman (1955)

Although the central nervous system stimulants are sometimes dramatic in their pharmacological effects they are relatively unimportant from a therapeutic point of view It is not possible to stimulate the nervous system over a long period of time, for heightened nervous activity is followed by depression, propor

tional in degree to the intensity and duration of the stimulation."

Nikethamide, Leptazol and Picrotoxin. The main pharmacological actions of these three drugs are summarised in Table L. It can be seen that all are cerebral stimulants and large doses produce convulsions. Lovibond and Steele (1939) have shown that picrotoxin is a more effective analeptic than nikethamide, the action of which is very transient. Moreover the use of large doses of nikethamide is not without danger especially in patients with a damaged myocardium. Its main value is as a respiratory stimulant in light anaesthesia for which purpose Lundy (1935) advocated combining nikethamide with thiopentone. Leptazol although having a quicker onset and being shorter acting than picrotoxin is a more potent cerebral stimulant. This prolonged action of picrotoxin may on occasions be a disadvantage, as Mousel and Essex (1941) have described the occurrence of convulsions for as long as 25 minutes after its injection. The combination of leptazol and barbiturates, for oral administration has been suggested by Koppanyi and Fazekas (1953) for the prevention of accidental barbiturate overdosage.

The effective dose of nikethamide varies from 2 to 5 ml. repeated as frequently as necessary. Leptazol is given in 3 to 5 ml doses at 5 to 10 minute intervals. This dosage can be increased if there is no response from the initial injections. A continuous infusion of 1 to 2 mg picrotoxin per minute can be employed or single doses of 3 to 6 mg are given at intervals of 15 to 30 minutes.

The intermittent method of administration is preferred, since this allows adequate time for its full effects (including convulsions) to become manifest.

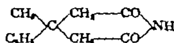
a **Lobeline** is the chief constituent of lobelia (Indian tobacco). Its main actions resemble those of nicotine causing an initial stimulation, followed by depression, of all sympathetic and parasympathetic ganglia. The respiratory and vomiting centres are stimulated, but it also acts on the carotid bodies. Lobeline has some vogue as a respiratory stimulant, especially for resuscitation of the newborn. Its effects are very variable and transient.

Megimide (N.P. 13). The value of this drug as a barbiturate antagonist was first demonstrated by Shaw *et al* (1954). It is

TABLE I.—*Summary of the main pharmacological actions of*

Name	*Chemical Structure or Botanical Source*	
NIKETHAMIDE (Coramine) (Nicamide) (Anacardone) (Corvotone)	CO N$(C_2H_5)_2$ N	Diethylamide of pyridine-3-carboxylic acid (M.W. 178·2)
LEPTAZOL (Metrazol) (Cardiazol) (Pentylenetetrazol) (Phrenazol)	H_2 H_2 C—C N—N H_2C C N N C—C H_2 H_2	1 5 pentamethylene-tetrazole (M W 138·2)
PICROTOXIN (Cocculin)	$C_{30}H_{34}O_{13}$	Active principle obtained from the seeds of Anamirta cocculus.
AMPHETAMINE (Benzedrine) (Allodene) (Isomyn) DEXAMPHETAMINE (Dexedrine) (Dexamed) (Daphraden)	CH_2 *CH* *CH_3* NH_2	*β-phenylisopropylamine* (M.W. 368 5). Dextro-form has about twice the potency of the racemic preparation.
METHAMPHETAMINE (Desoxyephedrine) (Methedrine) (Desoxyn)	CH_2 CH CH_3 NH CH_3	Methyl derivative of amphetamine.
DIGOXIN	$C_{41}H_{64}O_{14}$	Crystalline glycoside *from* Digitalis lanata.
OUABAIN (Strophanthin G)	$C_{29}H_{44}O_{12}$ $8H_2O$	Crystalline glycoside from wood of Acokanthera Schimperi and seed of Strophanthus gratus.

ββ methyl-ethyl glutarimide and has the following structural formula



Animal experiments have shown that it significantly reduces the period of narcosis with thiopentone and pentobarbitone. It has a marked stimulating action on respiration and when injected alone in very large doses produces convulsions which can be controlled by thiopentone.

A clinical trial of the value of megimide in reversing thiopentone narcosis has been reported by Harris (1955) In 73 subjects he found that 50 mg resulted in a rapid return of the corneal reflex and frequently they were talking within a few minutes. It was noted that after recovery the subject often lapsed into sleep again, but this was natural sleep from which they could be easily wakened by external stimuli. There were no fasciculations or any other side-effects observed after a single 50 mg dose of megimide.

A combination of megimide and Daptazole (2 4-diamino-5 phenylthiazole) was administered by Montuschi and Wickenden (1955) to a patient who had taken 39 gr (2 6 g) each of quinal barbitone and amylobarbitone. Treatment was started nearly twenty four hours after the barbiturates had been taken. Over a period of five hours megimide 2 g and daptazole 600 mg were given by intermittent injection, resulting in a return of the corneal reflex and strong coughing

The most extensive report on the use of megimide in barbiturate intoxication is that of Shulman, Shaw Cass and Whyte (1955). There was only one fatality in 41 patients, one-fifth of whom were seriously ill and in deep coma. In some cases megimide was combined with daptazole, which was found to be a powerful respiratory stimulant. Their treatment combined a regime similar to that advocated by Nilsson (1951) with intermittent *injection of megimide 50 mg and daptazole 15 mg every three to* five minutes until the patient reached a safe state The largest effective single dose of megimide used in one treatment was 2 g with 620 mg daptazole. The largest effective overall doses used in one patient were 5 49 g megimide and 1·7 g daptazole. Regression of consciousness was most common when an overdose of a long-acting barbiturate had been taken. From their experi

ences, Shulman *et al* concluded that the specific treatment with megimide and daptazole is quickly effective in reversing the most severe circulatory depression accompanying barbiturate intoxication.

Vomiting and retching is usually the earliest, and is frequently the only clinical sign of incipient toxicity from the above regime This may be followed by slight flickers of the fingers treatment should be momentarily suspended and a small dose of 2 5 per cent. thiopentone prepared in case convulsions occur Overdosage is manifested by excessive excitement and restlessness on subsequent wakening and can be effectively reversed by sedation with paraldehyde or a barbiturate such as quinalbarbitone or amylobarbitone.

Multiple Vitamin-Glucose Mixture The analeptic value of this mixture has been suggested by the part played by glucose and vitamins in brain metabolism. Gould (1953) has recommended the following combination

Glucose 10 g (10 per cent. solution)	100 ml.
Aneurine hydrochloride	1000 mg
Nicotinamide	200 mg
Pyridoxine	200 mg
Ascorbic acid	1500 mg
Distilled water or normal saline to	250–300 ml.

The total volume is given in 40 to 70 minutes, or the same quantities of the vitamins can be given intravenously in 30 to 50 ml. of 10 per cent. glucose. Gould has reported the use of the above in two cases of barbiturate coma, with a prompt recovery in both patients. An equally dramatic awakening occurred when the mixture was used in coma due to a number of drugs which included paraldehyde and hyoscine. Other workers have found it of value in the detoxication of drunkenness and good results have been claimed for the use of vitamin B_6 alone in this condition.

SYMPATHOMIMETIC AMINES

Amphetamine and its dextro-isomer combine a cerebral stimulant action with the ability to maintain the blood pressure (Table L) Their administration has been advocated in barbiturate poisoning but the chief therapeutic application of their central

stimulant action appears to be in the treatment of narcolepsy and postencephalitic parkinsonism (Goodman and Gilman, 1955).

Methamphetamine is used more widely for its vasopressor action than for its cerebral stimulant effects. This latter may even be a disadvantage when the effects of the drug persist into the post-operative period. Its most common use is in combination with spinal analgesia, but it has been suggested that it be mixed with thiopentone to prevent the hypotensive action of the anaesthetic (Lockett, 1951) The dose for a single intravenous injection ranges from 5 to 15 mg and for an intramuscular injection a dose of 10 to 30 mg is recommended Dodd and Prescott (1943) found that the maximum effect occurred in 2 to 18 minutes and persisted for several hours. A single parenteral injection of methamphetamine cannot produce as controllable an effect as a continuous infusion of *l* noradrenaline. Furthermore if a single-dose drug is desired, it seems advisable to use a preparation, the main action of which is to cause peripheral vasoconstriction and increase the total peripheral resistance, while having little effect on the heart.

Methoxamine appears to fulfil the above criteria. The onset of the pressor action is almost immediate after intravenous injection, and persists for about an hour The dose should not exceed 10 mg It causes little or no cerebral stimulation.

Phenylephrine also has little effect on the heart. The duration of an effective intravenous dose (0·5 mg) is about 20 to 30 minutes. Accompanying the pressor action is a pronounced and persistent bradycardia. Like methoxamine, its action is predominantly on the cardiovascular system and it does not cause cerebral stimulation. It is suggested that either methoxamine or phenylephrine are more suitable for combination with, or administration after thiopentone than methamphetamine.

CARDIAC GLYCOSIDES

Digoxin and Ouabain. These are included in Table L, since it is believed that, if a cardiac glycoside is required immediately before or during operation these are the most suitable preparations. Goodman and Gilman (1955) state that the action of ouabain begins within 3 to 10 minutes after its intravenous injection its maximum effect is observed within ½ to 2 hours and

lasts up to 8 to 12 hours after administration The action has completely worn off within 1 to 3 days Digoxin is slightly slower in onset of action and the maximum effect is not obtained until between 1½ to 5 hours after injections While its action persists for about the same length of time as that of ouabain an effect may still be observed up to 2 to 6 days after its use With digitalis or digoxin on the other hand the maximum effect does not occur until between 4 and 12 hours after administration and digitalisation remains complete for 2 to 3 days These latter glycosides would be quite useless for the rapid preparation of a patient for operation

Digitalisation can usually be achieved with between 0·75 and 1 mg of digoxin the comparable requirements of ouabain being 0 3 to 0·5 mg

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CHAPTER XII

IN RETROSPECT

"Wrong conclusions drawn from correct facts are sometimes the fault of the author and sometimes the fault of the reader Wrong conclusions may cause a doubt as to the safety of an anaesthetic drug or method" (MCQUILLAN 1947)

SINCE thiopentone has been in clinical use for over twenty years, it is proposed to discuss some of the early literature on the drug in the light of present knowledge. There are many instances of wrong conclusions being drawn from correct facts, the best example being the report concerning the use of thiopentone at Pearl Harbour (Halford 1943) This has been dealt with fully on pages 145 to 148

As the result of numerous animal experiments, Reynolds (1939) was the first to point out that the organism is able to destroy or change to another form of barbiturate only a certain amount of Pentothal over a given period of time. Part of the induction dose remains in the body and there is a cumulative action when additional doses are given This has been confirmed by many workers, and an *appreciation of this fact is essential* for the safe administration of thiopentone. However Reynolds suggested that the consistent and marked damage to the liver tissue may account for the cumulative action of Pentothal and for the unexpected action of fractional doses This was based on the finding by Reynolds Schenken and Veal (1938) of pathological changes in the liver in mice after thiopentone, which they wrongly assumed to be applicable to man. As the result of his observations on the cumulative action of thiopentone Reynolds concluded that the drug was not safe or desirable for prolonged anaesthesia. If we interpret this as referring to the use of thiopentone alone, it is in agreement with current views but if the drug is supplemented by an analgesic with or without a relaxant it has proved safe for prolonged anaesthesia.

Based on experience with 3810 consecutive administrations of thiopentone, Carraway (1939) remarked that he was unable to find a single contraindication to the use of Pentothal sodium The reliability of this observation must be considered in the light of

another of Carraway's statements, viz. that the drug caused no irritation of the subcutaneous tissues. Carraway and Carraway (1943) were still unable to find any contraindication to the use of thiopentone after 10,437 administrations performed on patients ranging from 2 to 92 years of age. However, they had one death in which they felt that the anaesthetic was a contributing factor. Thiopentone was used in combination with continuous oxygen in these patients and they considered that this technique generally left patients in a better condition at the end of the operation than at the beginning. They do not mention the duration of post-operative sleep which must have been very prolonged when thiopentone-oxygen was used alone for laparotomies. They stress, however, that the anaesthetist should never give more thiopentone than the patient's condition demands:

Anaesthetists will develop confidence in it and learn that it is not necessary to administer it continuously during the operation but only as the patient requires it. The amount to be administered cannot be calculated by any mathematical formula and if that method of administration is used one is certain to run into trouble. Pentothal-oxygen anaesthesia should be administered just as any other type, that is to give as little anaesthetic as is possible to keep the patient surgically anaesthetised.

After six and a half years' experience with thiopentone-oxygen anaesthesia Carraway and Carraway (1943) believed that this technique was associated with a lower morbidity and death rate than any other method of anaesthesia. They consider it a tribute to the safety of the technique that less than 1 per cent. of patients required any respiratory or cardiac stimulation while on the operating table!

In contrast to the Carraways' observation it is interesting to note that no fewer than 29 contraindications were mentioned in 28 reputable publications on thiopentone which appeared between 1941 and 1951. The most frequently listed conditions appear in Table LI. Many of these can be grouped under the heading "Inadequate Airway", whether this is present before operation or occurs during the operation. This group is now considered to be a contraindication to any type of anaesthetic. Liver and renal dysfunction are the next most frequently mentioned contra-indications, presumably based on the view that impairment of detoxication and excretion will result in very prolonged narcosis. While severe liver dysfunction can prolong the action of large

doses of thiopentone, it is only a relative contraindication t use (p 236) Unless it is accompanied by severe uraemia, disease does not preclude the use of thiopentone. All the pathological states listed in Table LI are conditions in w caution should be exercised in the use of thiopentone, but the not absolute contraindications to its use.

TABLE LI

Contraindications to thiopentone reported in 28 publications bet 1941 and 1951

Contraindication	No of Appearances in Literat		
	Absolute	Relative	Tot
Myocardial weakness	16	4	20
Liver dysfunction	14	5	19
Factors interfering with airway	16	2	18
Gross respiratory disease with dyspnoea	15	3	18
Oedema of glottis	16	1	17
Shock	9	7	16
Renal disease	9	4	13
Respiratory obstruction	8	2	10
Children under 10	5	4	9
Feeble elderly patients	5	4	9
Severe anaemia	8	1	9
Sepsis	3	3	6
Diabetes	2	4	6
Advanced malignant disease	3	2	5

When the sulphonamide drugs were introduced it was gested that a sulphur-containing narcotic should not be used anaesthesia in patients receiving these drugs. Adriani (1939) Lamson, Butler Dickison, Govier and Greer (1941) found subanaesthetic doses of thiopentone became anaesthetic and o lethal in animals which had received sulphonamide. Reports f many centres all over the world, especially dealing with mili surgery have described the safe simultaneous use of sulphonam and thiopentone. Nosworthy (1940) found no untoward happen during anaesthesia, even when the use of sulphapyridine produced a definitely blue coloration of the blood, and Smith (19 did not observe any deleterious effects from thiopentone in sold who had also been treated with sulphapyridine.

Although early reports from some centres described the use of thiopentone as the sole anaesthetic for abdominal surgery it was generally appreciated that it should not be used to produce muscular relaxation In the first publication on Barbiturate A Lundy (1935) recommended that local analgesia should also be used for abdominal incisions. Tuohy (1941) stated that it was comforting to know that the use of regional and intravenous anaesthesia together produced a method of anaesthesia which was safe and eliminated the explosion hazard Jarman (1937) and Kees (1941) advocated the use of spinal analgesia to produce muscular relaxation in combination with light thiopentone narcosis In spite of these views as recently as 1944 Adams stated that intravenous anaesthesia was comparatively safe for intra abdominal operations in certain selected cases for which spinal and inhalation anaesthesia were contraindicated but he did not recommend it as a routine procedure. Although it is difficult to reconcile this statement with current views one must remember that the use of diathermy in a subject who had a history of sensitivity to local analgesics limited the drugs available at that time to nitrous oxide, chloroform and intravenous barbiturates.

Two other statements in Lundy s first publication on thiopentone are worthy of mention He advocated topical analgesia in conjunction with thiopentone for bronchoscopy While recommending that ambulant patients should be able to walk without staggering before they are allowed to go home after thiopentone, he added in any case a friend should accompany the patient much as though his inebriation were alcoholic Failure to comply with this advice has recently led to several accidents (p 215)

Jarman and Abel (1936) in the first British reports commented that in their series of over 1000 cases no patient who had thiopentone alone vomited after operation although vomiting occurred in a very small proportion of those cases who had premedication in addition to thiopentone. This proportion however was no greater than that which followed the use of an opiate alone, and was much less than after inhalation anaesthesia. Although one is unlikely to anaesthetise a large series of patients with any agents and find no post-operative vomiting the incidence is lower after thiopentone than following inhalation anaesthesia (Table XXXIII) Of greater importance is the observation that the use of an opiate

as premedication is a major factor in the production of post operative vomiting

Wyckoff (1938) Lundy Adams, and Mousel (1939) and others recommended the use of thiopentone for dental operations, particularly in nervous patients or in those having an idiosyncrasy to local analgesic drugs It was not until 1940 that Bullard reported the dangers of this technique in patients in the upright position This omission is surprising since in 1936 Jarman and Abel remarked that owing to the fall in blood pressure with all intravenous barbiturates the recumbent posture is the safest for the administration of these anaesthetics Bullard also condemned the use of thiopentone in dental practice, where the operator was not properly equipped for dealing with the complications which may occur This latter is now considered to be an absolute contradindication to the use of thiopentone.

In conclusion, it is interesting to consider how thiopentone stands in relation to the requirements of the perfect anaesthetic as outlined by Morrin at the meeting of the British Medical Association in 1933 the year in which hexobarbitone was introduced. To appreciate the circumstances existing at that time it is first necessary to quote the following from the above paper

Further surgical progress can be accomplished if the anaesthetist can provide safe anaesthesia for the bad risks. Patients will submit more readily to surgical treatment when anaesthesia can be induced with safety in the amnesic patient. Good operative work depends on the complete muscular relaxation and normal respiratory rhythm of the perfectly anaesthetised patient, and satisfactory convalescence depends on freedom from post anaesthetic morbidity The necessity for the trained anaesthetist is more urgent than ever the casual anaesthetist is the patient s nightmare and the surgeon s purgatory The trained man is an essential unit in the modern surgical hospital.

The requirements listed by Morrin are

1 *Administration should be accompanied without discomfort to either the young or old patient, and without complicated apparatus*

The administration of thiopentone is simple and pleasant for the patient, but apparatus for the administration of oxygen and for suction should always be available.

2 *Induction must be agreeable and the anaesthetic should not have any deleterious effect on the respiration or circulation.*

Induction with thiopentone is extremely agreeable and while

the effects of the drug on respiration and circulation can be minimised by slow injection they can never be completely prevented

3 *Blood pressure should be maintained at a normal level throughout*

The effects of thiopentone on the blood pressure are largely dependent on the method of administration but one can never guarantee to maintain a normal blood pressure level Although postural hypotension is sometimes desired in modern anaesthesia this must be controllable a description which does not apply to that produced by thiopentone

4. *Elimination should be rapid without producing harmful effects on the hepatic, renal or pulmonary tissue*

Elimination of thiopentone from the body is slow but the removal of small doses from the nervous system is rapid in normal subjects The slow rate of detoxication is not a disadvantage provided the distribution of the drug in the body is understood In small doses thiopentone has no deleterious effects on the tissues named above

5 *The anaesthetic effect should be induced gradually and it should be at all times under control*

Anaesthesia can be induced at any desired rate with thiopentone, and with experience it is as easily controlled as that from any other agent.

6 *In addition to inducing sensory paralysis complete muscular relaxation should be rapidly and safely obtained*

Muscular relaxation which is never complete, can be rapidly but not safely produced by thiopentone. The modern concept of anaesthesia does not require a narcotic which will produce muscular relaxation since this cannot be obtained without respiratory depression Specific muscle relaxants of any desired duration are available, and these are non toxic if correctly used

Thiopentone does not produce complete sensory paralysis because it has virtually no analgesic properties and in this respect more than any other it fails to comply with the modern requirements of the perfect anaesthetic. Its other failures are due to the irritant action on the subcutaneous tissues and its depressant action on the myocardium

The alchemists of old sought in vain for the philosopher s stone which would have the power to transmute base metal into gold

The pharmacologist and anaesthetist today are seeking for the perfect anaesthetic, the requirements of which were admirably outlined by Shakespeare,[1] over three hundred years ago

Although it is not the perfect anaesthetic, if thiopentone is used by the perfect anaesthetist in combination with other suitable drugs, we shall approach the qualities of the potion possessed by the physician at the court of King Cymbeline.

> A drug of such damn d nature
> Will stupify and dull the sense awhile
> Which first perchance she'll prove on cats and dogs,
> Then afterwards up higher but there is
> No danger in what show of death it makes,
> More than the locking up the spirits a time,
> To be more fresh, reviving

1 *Cymbeline* Act I, Scene 5

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APPENDIX I

APPARATUS

It is not proposed to discuss the various orthodox types of syringes and needles which are available for intravenous injections but rather to describe some of the modifications of these and some of the apparatus which are frequently used in connection with intravenous anaesthesia

Third Hand. An extremely simple method of fastening a syringe to the arm has been described by Scott (1950) It consists of a bent safety pin and a rubber catheter (Fig 44) A further improve-

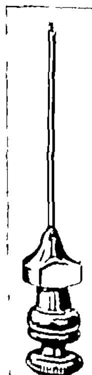


Fig. 44

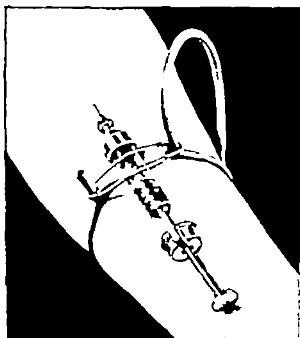


Fig 45 —" Third hand consisting of a bent safety pin and a urethral catheter (Scott 1950)

Fig. 44.—Cut down lumbar puncture needle and stillette for intravenous injection (Scott, 1950)

ment is to solder the pin in position This is light cheap and durable gives an unobstructed view of the syringe markings and permits easy adjustment of the tension.

Permanently Patent Needles Many methods have been described for ensuring that needles remain patent for repeated intravenous

injections. This can be achieved with reasonable certainty by the use of a continuous intravenous infusion but is not always practicable and on occasions the setting up of an infusion may be a more major procedure than the operation to be performed.

Stilettes The simplest form is a lumbar puncture needle cut down and bevelled (Fig 45). Guest (1941) has modified this by the addition of a cannula outside the needle (Fig 46) When the needle and stilette are removed the cannula can be used for an intravenous infusion and

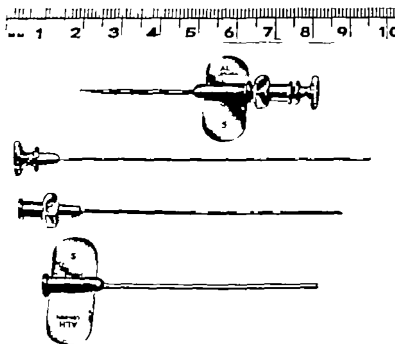


Fig. 46.—The Guest intravenous needle, adult and child size. (A. & L. Hawkins Ltd)

the blunt end is unlikely to pierce the vein wall. The Guest needle is available in adult and child sizes. Other similar cannulae and needles have been described such as the Franks Evans or the West Middlesex Hospital types.

Taps A simple tap can be inserted between the needle and syringe and stop the flow of blood into the needle. Halton has designed a three way tap (Fig 47) so that a drip apparatus may be used in conjunction with the intermittent injection of anaesthetic or relaxant drugs. Various modifications of the three-way tap have been described and Franks (19 4) has filed down the metal stop-pin on the piston thus allowing two infusions to be set up at the same time and run at independent rates

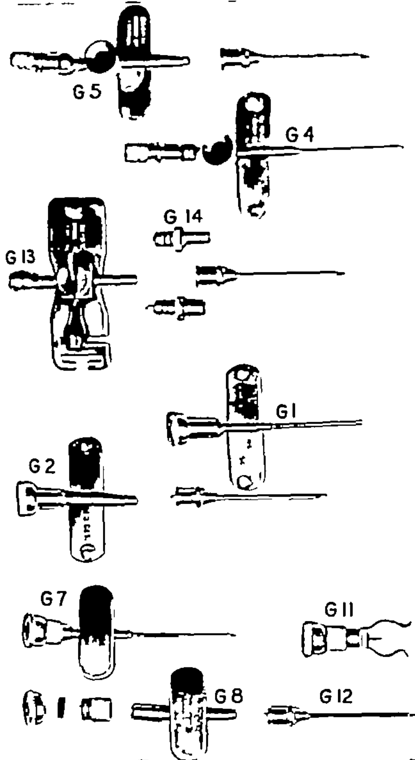


FIG 47 Various Modifications of the Gordh needle

G 1 Addition of shoulder wings
G 2 Diaphragm and shoulder wings made to fit standard Record or Luer needle (Robertshaw 949). A similar modification has been described by Forrester (949)
G 4 Gordh needle with modification for attachment t nfusion (A H. Musgrove).
G 5 As G 4, with diaphragm separate from needle
G 7 Gordh needle with push-on diaphragm (Rowbotham, 193)
G 8 As G 7 with diaphragm and wings separate from needle (G)
G 11 Diaphragm for clipping on transfusion tubing
G 13 Halton three-way tap.
G 14 Record fitting male and female adaptors for (3 (Blease Anaesthetic Equipment Ltd).

A Y shaped adaptor with taps at the distal ends is shown in Fig 48. This serves the same purpose as the three way tap Miller (1952) has interposed a short length of five vinyl plastic tubing (internal diameter approximately 1 mm.) between the Halton three way tap and the needle (Fig 49). This allows one to see when the needle is in a vein

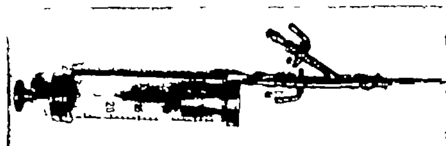


FIG. 48 —Y-shaped adaptor with taps at the distal ends. (Samrah, 1952)

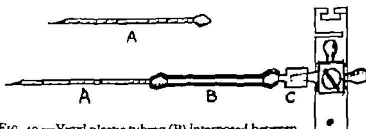


FIG 49.—Vinyl plastic tubing (B) interposed between the intravenous needle (A) and the three-way tap (C) (Miller 1952)



FIG 50 —Modification of the Frankis Evans needle and cannula. (Gould 1951)

without contaminating the tap and also makes fixation more simple. The Frankis Evans needle and cannula (similar to the Guest needle) has also been modified by the addition of a three way tap and flange (Fig 50).

Diaphragm The use of a rubber diaphragm mounted on a needle was first described by Olovsson, a surgeon in Stockholm for the repeated injection of heparin. Gordh (1945) drew the attention of anaesthetists to this needle which is now commonly known by his name Fox and Taylor described its use in this country in 1947 This needle and some of the many modifications which have been described are shown in Fig 47

The diaphragm is mounted at right angles to the long axis of the

adaptor in Fig 51 and two wings are malleable and can be mounted flush on the skin (Fig 52)

Self Sealing Fig 53 shows the needle designed by Mitchell (1952) The two top illustrations show the needle from above and from the side. The orifice lies in the wall 1 cm from the point The needle is solid distal to this opening When in position a light metal spring

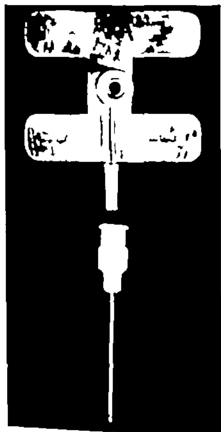




Fig. 52 —The modified Gordh needle in position. (Brennan 1951)

Fig 51 —Modified Gordh needle with two maleable wings and detachable needle (Brennan 1951)

bearing a soft rubber pad presses the skin and vein wall firmly against the needle thus occluding the orifice (bottom illustration)

For insertion the pad and spring are swivelled to one side and the correct position will be shown by a flow of blood or by aspiration into a syringe. The pad and spring are then swivelled back into the central position, an injection made to clear any blood and the syringe disconnected The needle remains securely fixed in place by the pressure of the rubber pad on the skin but this apposition may be reinforced by a small piece of adhesive strapping Injections can be made as required, merely by inserting the nozzle of the syringe into the hub of the needle fluid enters the vein with ease on injection but there is no reflux.

Remote Injections. Scurr (1948) has described the use of a long length of polythene tubing between the Gordh diaphragm and needle. This enables the arm to be placed by the side and repeated injections of solutions to be given as required. It is necessary to flush the polythene tubing with 2 ml. saline after each injection

Fig 54 shows a similar idea using a three way tap A continuous

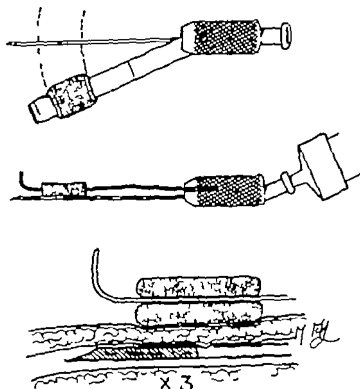


FIG. 53 —The Mitchell self-sealing needle (Mitchell, 1952)

intravenous infusion can also be given with this apparatus, while the arm remains at the side of the patient.

The apparatus described by Green (1954) consists of a small U shaped metal tube with a "male" Luer fitting at one end for connection to a Guest cannula or a standard transfusion needle, and a "female" Luer fitting at the other end to take the standard drip connection. To the centre of the U-shaped tube is connected a 30 inch (75 cm.) length of capillary tubing (capacity 1 5 ml) which has at the other end a Record adaptor with a non return valve (Fig 55). A cannula or needle is inserted into a convenient vein in the arm and the adaptor and transfusion set a[illegible]d (Fig 56). The infusion is then turned on and the

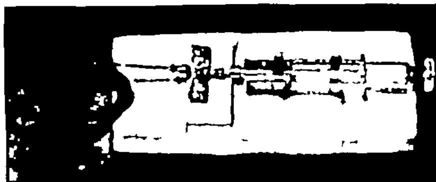


FIG. 54.—Apparatus for serial intravenous injections and continuous infusions. (Lee, J. A., personal communication)

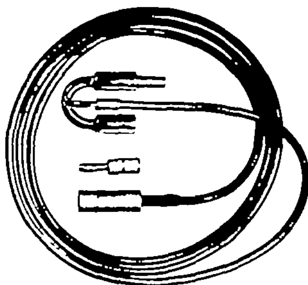


FIG. 55.—Capillary tubing and U-shaped metal adaptor for serial intravenous injections. (Green, 1954)

non-return valve is temporarily removed until all the air has been expelled from the capillary tubing. Intravenous injections, during the course of the anaesthetic, are made from the head of the patient, through the capillary tubing. After each dose of drug 2 ml. of saline are injected to wash the agent through to the vein.

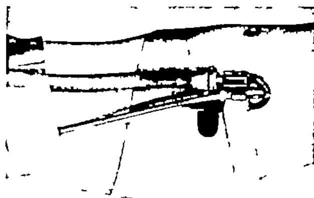


Fig. 56.—Green drip adaptor in position. (Green, 1954)

Syringe Container. Fig. 57 shows a container for storage and sterilisation of syringes described by Burns (1954). Support is given to the syringe by putting a "waist" in the glass tube, against which a

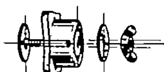


Fig. 57.—Syringe container. (Burns, 1954)



rubber cork rests. The nozzle of the syringe with mixing needle attached is inserted through one of two holes in this rubber cork. It is held firmly in position by the packing and rubber bung at the end of the glass tube. The tendency for the rubber bungs at the end of the tube to become loose after repeated autoclaving is overcome by the use of a me[illegible] expander. When the bung shrinks, the wing nut is t[illegible]tened s[illegible]t the two perforated metal plates are drawn together th[illegible] forces t[illegible]bber bung to expand outwards, and so a tight fit can st[illegible] be obt[illegible]. A dental throat pack fills the space between the syr[illegible]ge and [illegible]r bung and the tape is allowed to project slightly

from the bung so that the pack may be easily withdrawn without risk of desterilising the inside of the glass tube.

The container used at the London hospital (*Lancet* 1953) is shown in Fig. 58.

Syringe-Stand Barton (1953) has described the syringe stand shown in Fig. 59. Although ideally one should use a different size of syringe for each solution the addition of labels on the syringe stand

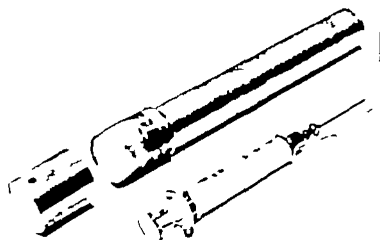


FIG. 58.—Container for sterilization of syringe and needle (Hospital Appliances Ltd.)

forms an extra safeguard against the injection of the wrong solution. A slightly more elaborate version of this stand known as the Whittington syringe stand has been described by Belam and Zuck (1953). The needles are protected from contamination by being suspended in a closed sterile chamber.

Other stands have been described which clip on to the anaesthetic machine and in which one syringe is placed above the other. These are frequently made from perspex or some similar transparent material. Where it is the practice to place syringes on the anaesthetic machine the risk of breakage from these rolling on to the floor can be minimised by the use of a sheet of corrugated rubber on which the syringes are placed.

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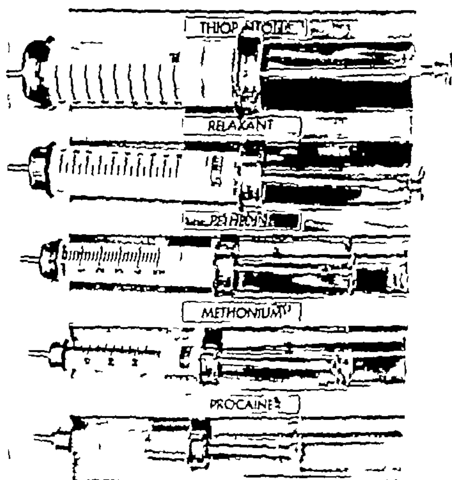


FIG. 59.—Syringe stand. (Barton, 1953)

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APPENDIX 2

COMPATIBILITY OF THIOBARBITURATES

ALTHOUGH it is not recommended that solutions of thiobarbiturates be mixed with other agents during anaesthesia the use of muscle relaxants in the same syringe has gained some popularity. Apart from the practice of mixing drugs, it is frequently necessary to use the same needle for injection as has been used for the thiobarbiturate. For this reason it is desirable to know the drugs with which a precipitate can be expected to form. This is of importance when there is a paucity of accessible veins and where blockage of a needle may have dire results.

The result of mixing the average clinical dose of various substances with 10 ml. 2·5 per cent. thiopentone is shown below. Because of the alkalinity of the thiopentone (pH 10·6 to 11·0) it will be seen that most strong acids form a precipitate. The pH of some of the substances tested is shown in brackets. However this is not the only factor and it must be appreciated that the term "compatible" as used below only refers to the absence of a precipitate on mixing with thiopentone. It does not necessarily mean that there has been no loss of potency of either drug. This is unlikely with thiopentone since the free acid is very insoluble in water but other compatible drugs may be hydrolysed. In some cases the precipitate which dissolves in excess of thiopentone may be inactive. This latter point has not been studied since the purpose of this appendix is simply to show what drugs can be injected through the same needle as a thiobarbiturate without the danger of blockage.

1. **Drugs used as premedication, or intravenous supplementation during anaesthesia.**

   Atropine sulphate (5·4)—compatible.
   Hyoscine Hydrobromine (Scopolamine) (5·1)—compatible.
   Opiates (3·5 to 4·0)—slight precipitate which dissolves in excess thiopentone.
   ANALGESICS
   Pethidine (5·4)—incompatible.
   Levophan tartrate (Dromoran) (6·0)—precipitate which dissolves in excess thiopentone.
   Nisentil (5·1)—incompatible.
   PHENOTHIAZINE DERIVATIVES
   Promethazine hydrochloride (Phenergan) (5·5)—incompatible.
   Chlorpromazine hydrochloride (Largactil) (5·3)—incompatible.
   Diethazine hydrochloride (Diparcol) (2·1)—incompatible.

2. **Hypotensive Drugs.**

   Hexamethonium bromide (3·95)—compatible.

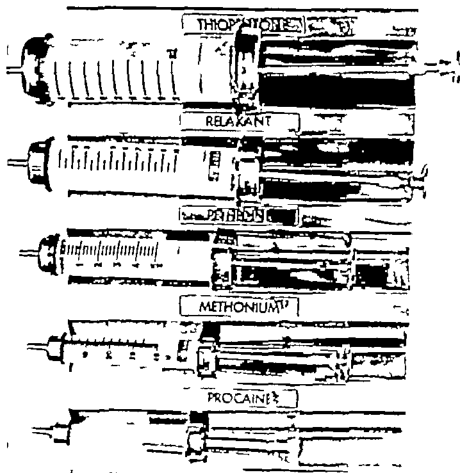


FIG 59.—Syringe stand. (Barton, 1953)

FRANKIS, E. H. (1954) *Brit. J Anaesth.* 26, 124.
GORDH T (1945) *Anesthesiology* 6 258
GOULD R. B (1951). *Anaesthesia*, 6 239.
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GREEN R. (1954). *Brit. J Anaesth.*, 26 287
Lancet (1953), 2, 237
MILLER, A. M (1952). *Anaesthesia*, 7 260.
MITCHELL, J V (1952). *Anaesthesia*, 7 258.
ROBERTSHAW F L. (1949). *Brit med J.*, 2, 96
ROWBOTHAM, E. S (1951) *Brit. med. J* 1 586.
SAMRAH, M E. (1952) *Brit J Anaesth.*, 24, 227
SCOTT D L (1950) *Anaesthesia* 5, 217
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COMPATIBILITY OF THIOBARBITURATES

Although it is not recommended that solutions of thiobarbiturates be mixed with other agents during anaesthesia the use of muscle relaxants in the same syringe has gained some popularity. Apart from the practice of mixing drugs it is frequently necessary to use the same needle for injection as has been used for the thiobarbiturate. For this reason it is desirable to know the drugs with which a precipitate can be expected to form. This is of importance when there is a paucity of accessible veins and where blockage of a needle may have dire results.

The result of mixing the average clinical dose of various substances with 10 ml. 2.5 per cent. thiopentone is shown below. Because of the alkalinity of the thiopentone (*p*H 10·6 to 11·0) it will be seen that most strong acids form a precipitate. The *p*H of some of the substances tested is shown in brackets. However this is not the only factor and it must be appreciated that the term "compatible" as used below only refers to the absence of a precipitate on mixing with thiopentone. It does not necessarily mean that there has been no loss of potency of either drug. This is unlikely with thiopentone since the free acid is very insoluble in water but other compatible drugs may be hydrolysed. In some cases the precipitate which dissolves in excess of thiopentone may be inactive. This latter point has not been studied since the purpose of this appendix is simply to show what drugs can be injected through the same needle as a thiobarbiturate without the danger of blockage.

1. **Drugs used as premedication or intravenous supplementation during anaesthesia.**

   Atropine sulphate (5·4)—compatible.
   Hyoscine Hydrobromine (Scopolamine) (5·1)—compatible.
   Opiates (3·5 to 4·0)—slight precipitate which dissolves in excess thiopentone.
   Analgesics
   Pethidine (5·4)—incompatible.
   Levophan tartrate (Dromoran) (6·0)—precipitate which dissolves in excess thiopentone.
   Nisentil (5·1)—incompatible.
   Phenothiazine Derivatives
   Promethazine hydrochloride (Phenergan) (5·5)—incompatible.
   Chlorpromazine hydrochloride (Largactil) (5·3)—incompatible.
   Diethazine hydrochloride (Diparcol) (2·1)—incompatible.

2. **Hypotensive Drugs.**

   Hexamethonium bromide (3·95)—compatible.

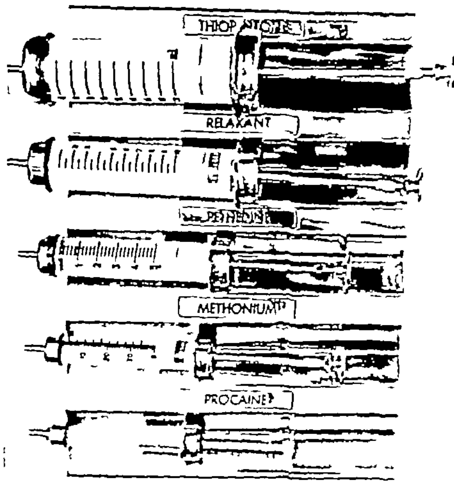


FIG. 59.—Syringe stand. (Barton 1953)

FRANKE, E. H (1954) *Brit J Anaesth.*, 26, 124.
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APPENDIX 2

COMPATIBILITY OF THIOBARBITURATES

ALTHOUGH it is not recommended that solutions of thiobarbiturates be mixed with other agents during anaesthesia the use of muscle relaxants in the same syringe has gained some popularity. Apart from the practice of mixing drugs, it is frequently necessary to use the same needle for injection as has been used for the thiobarbiturate. For this reason it is desirable to know the drugs with which a precipitate can be expected to form. This is of importance when there is a paucity of accessible veins and where blockage of a needle may have dire results.

The result of mixing the average clinical dose of various substances with 10 ml. 2·5 per cent. thiopentone is shown below. Because of the alkalinity of the thiopentone (*p*H 10·6 to 11·0) it will be seen that most strong acids form a precipitate. The *p*H of some of the substances tested is shown in brackets. However, this is not the only factor and it must be appreciated that the term "compatible" as used below only refers to the absence of a precipitate on mixing with thiopentone. It does not necessarily mean that there has been no loss of potency of either drug. This is unlikely with thiopentone since the free acid is very insoluble in water but other compatible drugs may be hydrolysed. In some cases the precipitate which dissolves in excess of thiopentone may be inactive. This latter point has not been studied since the purpose of this appendix is simply to show what drugs can be injected through the same needle as a thiobarbiturate without the danger of blockage.

1. **Drugs used as premedication, or intravenous supplementation during anaesthesia.**

   Atropine sulphate (5·4)—compatible
   Hyoscine Hydrobromine (Scopolamine) (5·1)—compatible
   Opiates (3·5 to 4·0)—slight precipitate which dissolves in excess thiopentone.
   ANALGESICS
   Pethidine (5·4)—incompatible
   Levophan tartrate (Dromoran) (6·0)—precipitate which dissolves in excess thiopentone
   Nisentil (5·1)—incompatible
   PHENOTHIAZINE DERIVATIVES
   Promethazine hydrochloride (Phenergan) (5·5)—incompatible.
   Chlorpromazine hydrochloride (Largactil) (5·3)—incompatible
   Diethazine hydrochloride (Diparcol) (2·1)—incompatible.

2. **Hypotensive Drugs.**

   Hexamethonium bromide (3·95)—compatible

Pentamethonium bromide (5·70)—compatible.
Pentolinium bitartrate (4·90)—precipitate which dissolves in excess thiopentone.
Arfonad 5 per cent. (5·70)—precipitate which dissolves in excess thiopentone.
5 per cent. thiopentone can be added to 0·1 per cent. Arfonad in 5 per cent dextrose or normal saline without visible precipitation.

Vasopressor Drugs.
Adrenaline tartrate (3 10)—incompatible.
Noradrenaline (3·20)—incompatible.
2 5 per cent thiopentone can be added to 1 200 000 solution of above in 5 per cent. dextrose or normal saline without visible precipitation.

Ephedrine sulphate (6·0) Methamphetamine (Methedrine) (6·15) Mephentermine sulphate (Mephine) (5 8) Methoxamine hydrochloride (Vasoxine) (4 1) Pholedrine (6·84)	precipitate which dissolves in excess thiopentone.

Amphetamine sulphate (6·5)—compatible.
Phenylephrine hydrochloride (6·4)—compatible.

4. **Muscle Relaxants.**
Gallamine triethiodide (6·66)—compatible.
Dimethyltubocurarine chloride (6·65)—compatible.
Dimethyltubocurarine bromide (6·21)—slight precipitate.
Mytolon chloride (5·6)—precipitate which dissolves in excess thiopentone.
Laudexium methosulphate (Laudolissin) (4 3)—incompatible.
Mephenesin (Myanesin) (5 1)—compatible.
D-tubocurarine chloride.

Three preparations were studied *d* tubocurarine chloride (Duncan) is compatible in all proportions normally used in anaesthesia. Tubarine (B W & Co) is immiscible in all dilutions likely to be of clinical use. Tubarine miscible (B W & Co) resulted in immediate precipitation when added to thiopentone (15 mg to 10 ml 2 5 per cent. thiopentone), but this dissolved within one minute.

Suxamethonium salts.

An immediate precipitate is formed which dissolved in excess thiopentone. On allowing a mixture of thiopentone and suxamethonium to stand hydrolysis of the relaxant occurs with a 50 per cent. loss of activity in 90 minutes (Fraser 1954).

5. **Analeptics.**
Nikethamide (6·45)—compatible
Picrotoxin (4 40)—compatible.
Leptazol (Metrazol) (7 5)—compatible

N.P. 13 (Megimide) (5·05)—compatible

Strychnine sulphate (5·9)—precipitate which dissolves in excess thiopentone

Nalorphine (2.6 to 2.7)—incompatible

Levallorphan (3.7)—precipitate which dissolves in excess thiopentone

Digoxin (7.25)—compatible

Strophanthin G (Ouabain) (5·9)—compatible

6. **Local Analgesics.**

Procaine hydrochloride—incompatible in all concentrations used for local analgesia but 0·05 to 0.1 per cent. solutions of the two drugs can be mixed without loss of potency of either

Lignocaine hydrochloride—0.5 to 2·0 per cent. solutions are precipitated by thiopentone but the precipitate dissolves in excess thiopentone. 0·1 per cent. lignocaine and 0·3 per cent. thiopentone cause a slight turbidity and 0·05 to 0·01 per cent. solutions of the two drugs can be mixed

Cinchocaine 1 : 1,500 (4.4)—incompatible.

7. **Miscellaneous.**

Benzodioxane (Piperoxan) (5·9)—precipitate which dissolves in excess thiopentone

Rogitine (Regitine) (3.4)—incompatible

Vitamin C—incompatible

Vitamin B_1—incompatible

Nicotinic acid—slight precipitate

Ergometrine maleate—compatible

Posterior pituitary extract (4.1)—precipitate which dissolves in excess thiopentone.

Pitressin (3.1)—precipitate which dissolves in excess thiopentone.

Aminophylline (9.4)—compatible

Priscol (5.1)—compatible

Papaverine sulphate (1·7)—incompatible

Calcium gluconate (6.3)—compatible

Sodium thiosulphate 50 per cent. (5.7)—compatible

Sodium nitrite (6·22)—compatible

Antistin (4.4)—incompatible

50 per cent. Diodine—incompatible

1 per cent. Protamine sulphate (2.9)—incompatible

Soluble insulin—compatible

Adrenoxyl (6·7)—compatible

Quinidine sulphate (3.7)—incompatible

REFERENCE

FRASER, I. J. (1954). *Brit. J. Pharmacol.* 9, 429.

Pentamethonium bromide (5·70)—compatible.

Pentolinium bitartrate (4·90)—precipitate which dissolves in excess thiopentone.

Arfonad 5 per cent. (5·70)—precipitate which dissolves in excess thiopentone.

2 5 per cent thiopentone can be added to 0·1 per cent. Arfonad in 5 per cent. dextrose or normal saline without visible precipitation

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Mephentermine sulphate (Mephine) (5 8)
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Pholedrine (6·84)
—precipitate which dissolves in excess thiopentone.

Amphetamine sulphate (6·5)—compatible

Phenylephrine hydrochloride (6·4)—compatible

4. **Muscle Relaxants.**

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Dimethyltubocurarine chloride (6·65)—compatible.

Dimethyltubocurarine bromide (6·21)—slight precipitate.

Mytolon chloride (5 6)—precipitate which dissolves in excess thiopentone.

Laudexium methosulphate (Laudolissin) (4 3)—incompatible.

Mephenesin (Myanesin) (5 1)—compatible.

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Picrotoxin (4 40)—compatible.

Leptazol (Metrazol) (7 5)—compatible.

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Strychnine sulphate (5 9)—precipitate which dissolves in excess thiopentone
Nalorphine (2 6 to 2 7)—incompatible
Levallorphan (3 7)—precipitate which dissolves in excess thiopentone.
Digoxin (7 25)—compatible
Strophanthin G (Ouabain) (5·9)—compatible

6. **Local Analgesics.**
Procaine hydrochloride—incompatible in all concentrations used for local analgesia, but 0·05 to 0 1 per cent solutions of the two drugs can be mixed without loss of potency of either
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Cinchocaine 1 1 500 (4 4)—incompatible

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Rogitine (Regitine) (3 4)—incompatible
Vitamin C—incompatible
Vitamin B_1—incompatible
Nicotinic acid —slight precipitate
Ergometrine maleate—compatible
Posterior pituitary extract (4 1)—precipitate which dissolves in excess thiopentone.
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Aminophylline (9·4)—compatible
Priscol (5 1)—compatible
Papaverine sulphate (1·7)—incompatible
Calcium gluconate (6·3)—compatible
Sodium thiosulphate 50 per cent. (5 7)—compatible
Sodium nitrite (6·22)—compatible
Antistin (4 4)—incompatible
50 per cent Diodine—incompatible
1 per cent. Protamine sulphate (2 9)—incompatible
Soluble insulin— compatible.
Adrenoxyl (6·7)—compatible.
Quinidine sulphate (3·7)—incompatible.

REFERENCE

FRASER, P J (1954) *Brit J Pharmacol* 9 429

METHODS OF DETECTION AND ESTIMATION OF THIOBARBITURATES

The underlying principles have already been discussed in Chapter II In the light of these criticisms detailed description of methods will be limited to a few reliable techniques.

ANALYSIS OF COMMERCIAL PREPARATIONS OF THIOPENTONE

The following are recommended in the British Pharmacopoeia (1953)

Identification

(1) On boiling with a strong solution of NaOH no ammonia is evolved. This distinguishes thiopentone from barbiturates.

(2) Dissolve 500 mg in 100 ml. water and acidify the solution with dilute HCl. Collect the precipitate on filter paper wash with water and dry at 70 C The melting point of the residue should be about 157 C

(3) Dissolve 100 mg in 10 ml. of 10 per cent. w/v solution of pyridine in water and add 1 ml. of solution of $CuSO_4$ treated with pyridine. A green precipitate is produced if the unknown substance is thiopentone.

(4) The residue left after incineration yields the reactions characteristic of sodium.

Assay

(1) For Sodium. Dissolve about 600 mg accurately weighed in 20 ml. water add one drop of methyl red indicator Titrate with *N/10* HCl until the yellow coloration turns to pink, boil gently for 2 minutes and allow to cool. If necessary continue the titration with *N/10* HCl until the pink colour is restored. Each ml. of *N/10* HCl is equivalent to 2 3 mg sodium.

(2) for 5-ethyl 5'(1 methyl butyl)-2 thiobarbituric acid. To the above liquid add a further 5 ml. *N/10* HCl and extract with successive quantities of 25 25 20 15 15 and 10 ml. chloroform. Dry the residue of 5-ethyl 5 (1 methyl butyl)-2 thiobarbituric acid to constant weight at 70 C and weigh

When an aqueous solution—as prepared for clinical use—is known to contain only the sodium salt of thiopentone and the sodium carbonate, its strength (w/v) can be estimated by ultra violet spectrophotometry The unknown and standards of 2 5 and 5 per cent. are diluted 1 10,000 transferred to quartz cells and the optical density determined at 288

mμ 0·06 per cent w/v solution of sodium carbonate (similarly diluted) being used as a blank This wavelength differs from that in the method to be described for estimation in biological material because of the lowered alkalinity due to dilution. The optical density is proportional to the strength of solution This method is applicable to thialbarbitone and thiamylal (Dundee 1954)

ESTIMATION OF THIOPENTONE IN BIOLOGICAL MATERIAL

The following method a modification of that described by Brodie *et al* (1950), is specific for thiopentone

Reagents. 1 N NaOH is prepared by dissolving 40 g NaOH pellets in 100 ml. distilled water 2 5 and 0·1 N solutions are prepared with 100 and 4 g NaOH respectively

1 N HCl contains 36·5 g HCl per litre Take (36·5 divided by the S G of concentrated stock solution) ml concentrated HCl and dilute to 1000 ml

1 5 Molar NaH_2PO_4 prepared from 181 5 g NaH_2PO_4 with distilled water to 1000 ml.

Petroleum ether (technical grade) should be washed successively with approximately one third their volume of 1 N NaOH 1 N HCl followed by two washings with distilled water Reagent grade isoamyl alcohol is added to the petroleum ether

Blood or Plasma. The technique is equally applicable to blood or plasma.

Add 1 ml. of fluid 1 ml 1 5 Molar NaH_2PO_4 and 30 ml petroleum ether containing 1 5 per cent isoamyl alcohol to a 60 ml glass stoppered bottle. Shake for one hour and centrifuge if necessary

Transfer as much as possible of the supernatant organic solvent phase to another glass-stoppered bottle containing 15 ml 1 5 Molar NaH_2PO_4 Shake for two minutes.

Transfer 20 ml. solvent phase to another glass stoppered bottle containing 5 ml. 2 5 N NaOH Shake for two minutes.

Remove the supernatant solvent phase by aspiration

Transfer 3 ml. of the aqueous phase to a quartz cuvette and determine the optical density at 305 mμ in an ultraviolet spectrophotometer

Urine Add 1 ml. urine 1 ml 1 5 Molar NaH_2PO_4 0·25 g NaCl and 30 ml. petroleum ether to a 60 ml glass-stoppered bottle. Shake for 5 minutes and centrifuge

Transfer 20 ml. of the supernatant solvent phase to a 60 ml. glass stoppered bottle containing 5 ml 2 5 *N* NaOH

Continue as described for the estimation of thiopentone in blood or plasma

Reagent blanks are run through the same procedures. They should not read more than 0·010 when 2 5 *N* NaOH is used for the zero setting

A **Standard** solution, containing 100 mg thiopentone per 1000 ml.

is prepared by dissolving 92 mg 5-ethyl 5 (methyl butyl)-2 thiobarbituric acid in 3 ml. of 0·1 *N* NaOH and diluting to 1000 ml. with distilled water Thiopentone is unstable in alkaline solution, so that this stock solution must be freshly prepared just prior to use. Working standards are prepared by dilution of 1 ml. above with an appropriate volume of 2·5 *N* NaOH A concentration of 50 mg per litre has an optical density of about 0·726 (standard reading minus reagent blank).

Calculation. The reading for the plasma blank is subtracted from the optical density of the unknown solution.

The corrected optical densities of the known and unknown solutions are proportional to their concentrations.

Tissues. Organs are prepared for analysis by emulsification in water as described by Brodie, Udenfriend and Baer (1947) Fat samples are emulsified in 0·1 *N* NaOH to extract the thiopentone into an aqueous phase. Add 1 to 5 ml of homogenized tissue and an equal volume of 1·5 *M* NaH_2PO_4 to a 60-ml. glass-stoppered bottle which contains 30 ml petroleum ether (technical grade) containing 1·5 per cent. isoamyl alcohol Shake for 1 hour and then continue as described above for the estimation of thiopentone in plasma. The optical density of alkaline solution of the unknown (U) and standard (S) are read at 305 mμ (*a*) and 330 mμ (*b*).

The thiopentone concentration in the solution to be measured is calculated from the formula

$$\frac{Ua-Ub}{Sa-Sb}\times C$$

C is the concentration of thiopentone in the standard. This correction for the blank depends on the fact that its optical density at 305 mμ and 330 mμ is to all practical purposes the same, whereas that for thiopentone decreases by about 90 per cent. Brodie *et al.* (1950) have also described a method of determination of thiopentone carboxylic acid, a metabolite of thiopentone in urine. This compound is negligibly soluble in petroleum ether but may be extracted with ethylene dichloride.

Rayburn, Whitehead and Draper (1953) have described a simpler method of extraction of thiopentone from plasma, using ethylene dichloride. This does not distinguish between thiopentone and its carboxylic acid derivatives.

1 ml. plasma, 15 ml. ethylene dichloride and 2 ml. 1·5 Molar NaH_2PO_4 are shaken for 10 minutes, followed by centrifuging at 4000 revolutions per minute for a further 10 mins.

10 ml. of the organic solvent phase and 5 ml 2·5 *N* NaOH are mixed for 10 minutes, followed by centrifuging for 10 minutes.

3 ml aqueous phase are transferred to a quartz cuvette and the optical density read at 303 mμ.

Blank and standard determinations and calculations are carried out as for the previous method of analysis.

APPENDIX 4

CASE REPORTS OF RESISTANCE TO THIOBARBITURATES

THE following instances of resistance to thiopentone or other thiobarbiturates have been encountered personally by the author or colleagues.

Case 1. Mrs. A. A., aged 32, weight 112 lb. (50 kg.). The patient had been taking large doses of barbiturates and bromisovalerylurea for several months. Operation was for prefrontal leucotomy.

Premedication was with papaveretum ⅓ gr. (21 mg.) and scopolamine $\frac{1}{150}$ gr. (0·42 mg.). Anaesthesia was induced with 700 mg. thiopentone and oral intubation carried out after topical application of 2 per cent. amethocaine to pharynx and larynx. 1 g. thiopentone was required before the patient could be placed on the operating table. Maintenance of narcosis was with nitrous oxide/oxygen/trichlorethylene and intermittent injection of thiopentone and pethidine.

During the operation, which lasted 90 minutes, a total of 1·65 g. thiopentone and 80 mg. pethidine were given. The patient was fully awake on return to the ward.

Case 2. Dr. L., aged 54, weight 156 lb. (71 kg.). Extensive thrombosis of one leg was followed by a below knee amputation. A slough on the medical aspect of the thigh had been excised and a skin graft applied. Because of severe pain in the stump the patient had been taking 700 to 800 mg. pethidine daily for the past three weeks. Anaesthesia was required for examination of the skin graft and amputation stump.

No premedication was given. Induction was with 5 per cent. thiopentone, 900 mg. being given before the bandage could be removed from the skin graft. A further 500 mg. (with nitrous oxide/oxygen) was required during the first 7 minutes of anaesthesia, which was continued with cyclopropane and oxygen.

Case 3. Miss R. J., aged 62, weight 140 lb. (63 kg.). The patient had been taking various compounds containing acetylsalicylic acid on and off for several years for the relief of trigeminal neuralgia. Recently these had proved ineffective even in very large doses. Operation was for trigeminal root section. Premedication was with morphine ⅙ gr. (10 mg.) and atropine $\frac{1}{100}$ gr. (0·65 mg.). Anaesthesia was induced with thiopentone 500 mg. and suxamethonium 40 mg. and an armoured oral endotracheal tube passed under direct vision. Intubation was followed by violent coughing and thiopentone to a total of 1 g. was required before the patient settled. When the head of the table was raised, severe postural hypotension occurred. Recovery took place when the head was lowered. The operation was postponed and carried out one week later under local analgesia.

Case 4. Mrs. L. H., aged 49, weight 154 lb. (70 kg.). She complained of hypretensive headaches for over one year and had been receiving thrice-daily doses of ½ gr. (32 mg.) phenobarbitone. For the past 6 to 7 months she had also been taking potassium bromide 15 gr. (1 g.) and chloral hydrate 15 gr. three to four times daily. B.P. was 240/150. Sedation with 9 gr. (600 mg.) amylobarbitone had very little effect on the blood pressure. Operation was for thoraco-lumbar sympathectomy.

Premedication was with promethazine 50 mg. and pethidine 100 mg.

Anaesthesia was induced with 30 mg *d*-tubocurarine chloride followed by the slow injection of 400 mg thiopentone. Oral intubation was carried out with difficulty and the respiration seemed to be little affected by the relaxant. Pethidine 25 mg was given and as coughing continued this was followed by a further 200 mg thiopentone and 10 mg *d*-tubocurarine chloride. Anaesthesia was continued with 1 litre nitrous oxide and 1 litre oxygen per minute with controlled respiration and CO_2 absorption. Before the skin incision was made a total of 1 g thiopentone was required.

Coughing occurred several times during operation and a further 250 mg thiopentone, 50 mg pethidine and 15 mg *d*-tubocurarine chloride were required. Severe hypotension occurred during the operation but was controlled by infusion of 1 : 250 000 *l*-noradrenaline. Recovery from anaesthesia was prompt but severe hypotension persisted for more than 24 hours.

Case 5. Mrs A X aged about 35, weight 119 lb (54 kg). Admitted to hospital with severe lower abdominal pain, dysuria and haematuria. Patient was given 1/4 gr (15 mg) morphine soon after admission and 1/100 gr (0·65 mg) atropine was administered 3 hours later, prior to cystoscopy. Anaesthesia was induced with 400 mg thiamylal which had little effect on the patient. Over 1 g thiamylal was required before the cystoscopy could be carried out. A self-induced abrasion of the urethra was discovered with a foreign body in the bladder. The total operating time including removal of the foreign body was about 20 mins., during which period almost 1·5 g thiamylal was required with nitrous oxide/oxygen trichlorethylene. It was later discovered that the patient was a drug addict and had been admitted to hospitals all over the country during the past few years. On each occasion she was found to have apparently self-inflicted lesions and complained of very severe pain requiring opiates or similar drugs. She had had at least three previous minor operations, at one of which the anaesthetist administered thiopentone but recalled no abnormality in the dosage. On another occasion, for incision of an abscess she was reported to have been "barely asleep following 500 mg thiopentone given very quickly." On the third occasion no barbiturates were given but she proved to be extremely resistant to the drugs used.

All the above cases of resistance could be due to an acquired tolerance to sedative or analgesic drugs. In cases 3 and 4 the resistance was only to the central effects of the drugs as cardiovascular collapse occurred for which at least part of the blame must be placed on the large doses of thiopentone. In the next two cases there was an acquired tolerance to opiates but resistance to thiopentone was not obvious.

Case 6. Mr H T aged 42, weight 133 lb (60 kg). History of passing stones per urethra for several years with severe attacks of renal colic. Before admission to hospital 1 gr (65 mg) morphine was required to relieve the colic and for three months the patient had been taking this nightly. Operation was for removal of vesical calculus. Premedication was morphine 1/4 gr (15 mg) and atropine 1/150 gr (0·4 mg). Anaesthesia was with nitrous oxide/oxygen and intermittent doses of thiopentone. During the whole procedure lasting 45 minutes, a total of 500 mg thiopentone was administered. Consciousness was not regained until 5 hours after the end of the operation.

Questioned the following day, the patient admitted taking 1 gr morphine orally early in the morning of operation, and the same dose 3 hours before operation. He was not unduly drowsy before induction and the self-administration of opiates was not suspected.

Case 7. Mrs. E McM aged 73, weight 162 lb (73 kg). History of frequent attacks of vomiting and malena within the past four weeks. Severe epigastric pain was relieved by frequent injections of morphine, the daily dose before operation averaged 1·5 gr (100 mg). Details of the anaesthetic are incomplete but papaveretum 2/3 gr (42 mg) and scopolamine 1/150 gr (0·42 mg) were given

4 hours prior to operation (for a preliminary gastroscopy under local analgesia). This was repeated in error 1 hour before the subsequent gastrectomy. A total of 650 mg. thiopentone and 35 mg. *d* tubocurarine with chloride nitrous oxide/oxygen sufficed for an operation lasting 135 minutes. Recovery was not delayed.

The administration of large doses of sedative to these patients immediately before induction of anaesthesia may well have prevented obvious resistance to thiopentone. In spite of the large doses of opiates given neither of these two patients exhibited an undue drowsiness before operation or the sensitivity to thiopentone which would have been expected to follow their use in normal subjects.

In case 8 marked resistance to thialbarbitone was encountered and no explanation can be offered other than alcoholic addiction. In case 9 addiction to cannabis indica (hashish) is the most likely cause of resistance.

Case 8. Sergeant R. S., aged about 35, weight about 154 lb. (70 kg.). Admitted to hospital with Colles fracture, which was reduced under brachial plexus block because of his state of alcoholic intoxication. For a plaster change 18 hours later 1 g. thialbarbitone was given and did not induce sleep. A total of 3 g. was required with nitrous oxide/oxygen/methyl-n-propyl ether for a procedure lasting about 5 minutes, and the patient was muttering incoherently within another 2 minutes.

Case 9. Mr. S. D., a coloured patient aged about 45, weight 160 lb. (73 kg.), attended hospital frequently for urethral dilatation. His resistance to anaesthetics was well known and appeared to increase with each successive administration. The following are a few examples:

Thiopentone 600 mg.—laughing and coughing violently.
Thiopentone 500 mg. with pethidine 30 mg.—coughing violently, difficulty in applying face mask.
Thiamylal 400 mg.—laughing.
Thiamylal 800 mg. given quickly enabled one bougie to be passed. Walking around ward in 5 minutes.
Thialbarbitone 3000 mg. given intermittently over 10 minutes for difficult bouginage. Coughing and laughing immediately on return to ward.
Thiopentone 900 mg. and gallamine triethiodide 120 mg. given for incision of abscess. Recovered within 5 minutes.
After repeated questioning as regards drug addiction he admitted to smoking "reefers" (hashish).

In case 10 there was not only resistance to thiopentone but also to pethidine and *d* tubocurarine chloride. No cause for this tolerance could be found, although, because of the subject's occupation, alcoholic tolerance seems most likely.

Case 10. Male, aged 43, weight 134 lb. (59 kg.), for repair of indirect inguinal hernia, no symptoms or signs of other disease.

Premedication: papaveretum gr. ⅓ (21 mg.), scopolamine gr. 1/150 (0.42 mg.) by I.M. injection.

Anaesthetic—Thiopentone 200 mg. had no effect; further 250 mg.—patient yawned; further 300 mg.—closed eyes; 15 mg. *d* tubocurarine chloride given. Resisted nitrous oxide/oxygen (7 l.: 3 l/min.)/trichlorethylene added one minute after application of the mask. 1 per cent. pethidine 50 mg. I.V. had no detectable effect—further 15 mg. *d*-tubocurarine chloride and 50 mg. pethidine were given and he became quieter but still showed resistance. After 4 minutes struggling in N_2O/O_2, trichlorethylene a further 50 mg. pethidine and 15 mg. *d*-tubocur[illegible] chloride were given. Before the skin-clips were placed, as

there was some reaction to skin preparation another 15 mg. *d*-tubocurarine chloride and 250 mg. thiopentone was required (Total drugs before operation —thiopentone 1000 mg., pethidine 150 mg., *d*-tubocurarine chloride 60 mg.)

The operation lasted 25 minutes At no stage did the respiratory rate fall below 20 min., nor was any assistance to respiration required The trichlorethylene was turned off at the last skin stitch the patient helped to remove the mask as the strapping was put on Within 10 minutes of return to the ward he required ½ gr. (32 mg.) morphine to control extreme restlessness

All drugs were stored at room temperature away from sources of heat and supplies from the same batches of drugs had been used on three previous cases and on two succeeding ones without any abnormal responses All thiopentone pethidine *d*-tubocurarine chloride were without doubt given intravenously Patient was a liner steward who denied any drug addiction including alcohol: during his remaining 10 days in hospital he did not display any evidence of addiction, or withdrawal symptom All D.D.A. drugs in the hospital at this time were carefully controlled and checked and there were no discrepancies

In a lighter vein may be added the following report It should serve as a warning against drawing too hasty conclusions concerning resistance to thiobarbiturates

A healthy male aged 28 years and weighing about 176 lb. (80 kg.) was admitted for repair of a left inguinal hernia It was decided that the anaesthetic should be administered by a student under supervision the induction to be with 5 per cent thiopentone followed by nitrous oxide oxygen ether All preparations for the administration were made by the student After 10 ml. thiobarbiturate were given slowly the patient said he felt sleepy and he closed his eyes after a further 4 ml. but opened them when the face mask was applied After 20 ml. were given, nitrous oxide oxygen ether was started but the subject was very obstreperous. The needle was reinserted into a vein and slow administration of the drug continued It was not possible to continue with the inhalation agents until a total of 64 ml. had been given There appeared to be no reason for the patient's resistance as the record of an anaesthetic given five months previously for repair of a hernia on the right side showed the total dose of thiopentone to have been 600 mg. The preparation of the solution was checked and the student mentioned having heard that the use of a 2.5 per cent. solution increased the safety of thiopentone Even this did not settle the matter as 1.4 g. thiopentone seemed a large dose to induce anaesthesia The remaining solution was removed with a view to having it analysed—80 ml. having been prepared. A rough check on a spectrophotometer showed the strength of the solution to be approximately 2½ per cent

The problem remained unsolved for several weeks when the same student about to administer another anaesthetic, was seen to take a 2 g. ampoule of thialbarbitone and dilute it to 80 ml. On questioning, it transpired that he was under the impression that Kemithal was a proprietary name for thiopentone He had used it on the previous occasion as he thought he was doing everyone a good turn by making up 2 g. at once

THE CLEANSING AND STERILISATION OF SYRINGES

MOST workers prefer all-glass syringes as metal is apt to retain particles of blood. The former have a tendency to break at the nozzle and sometimes there is difficulty in obtaining a tight fit between syringe and needle. Glass syringes with metal nozzles, made from an alloy which has a similar coefficient of expansion to that of glass, have the advantage of a stronger nozzle. However Burns (1952) has pointed out that the cement between the metal and the glass tends to disintegrate with repeated sterilisation and leaves a space for the blood to accumulate.

Cleaning Syringes should be rinsed in cold water immediately after use to prevent the clotting of aspirated blood. The barrel and plunger are washed in warm soapy water and dried with a fluffless cloth (M R.C 1954). Gibson (1951) suggests the application of surgical spirit as an alternative method of drying

Needles are cleaned separately from the syringe. They are rinsed in cold water immediately after use and the mount is cleaned with cotton wool on a swab stick. The needles are then washed through again first with water then with alcohol (industrial methylated spirit) and allowed to dry The stilette is lubricated with a minimum of liquid paraffin before passing through the needle.

Lubrication. Before assembly the piston is lightly lubricated with liquid paraffin, which is well rubbed in with the finger Darling and Spencer (1951) point out that the use of liquid paraffin is invariably followed by some degree of charring on sterilisation and they advocate silicone D C 550 for lubrication. The water repellent properties of silicone make cleaning difficult. To overcome the disadvantages of liquid paraffin all of which arise from its excessive use, mixtures of one part with two parts ether (Dunbury 1951) one part with four parts methylated spirit (Gibson, 1951) and 1 ml. added to 1 lb trichlor ethylene (Trilwood, 1951) have been recommended

Assembly A needle is mounted on each syringe and the outfit placed in a suitable container before sterilisation. The Medical Research Council (1945) recommended suspending the syringe in a test tube and wrapping the tube with syringe in position in kraft paper Many modifications of or alternatives to this method have been described and those shown in Figs. 57 and 58 seem to be the most satisfactory

Sterilisation. This is effected by placing the containers in a hot-air steriliser and maintaining at 160 C. for not less than one hour The temperature should be checked from time to time to ensure that effective sterilisation is being carried out and syringes should be allowed to cool before removal from the steriliser As an alternative they can be

autoclaved (15 to 20 lb. pressure) at 120° C. for at least twenty minutes (M.R.C. 1945).

Swiss workers suggest that the temperature should reach 180° to 200° C. during dry sterilisation. They also suggest boiling under pressure as an alternative to the methods described above (Baumann, 1948).

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